Synthetic studies towards the pyrrolo[2,1-*c*][1,4]benzodiazepine natural products

A thesis submitted for the degree of Doctor of Philosophy of

The Australian National University

by

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Declaration

I declare that, to the best of my knowledge, the material presented in this thesis represents the result of original work carried out by the author during the period 2008-2011 and has not been presented for examination for any other degree. This thesis is less than 100,000 words in length. Established methodologies have been acknowledged, wherever possible, by citation of the original publications from which they derive.

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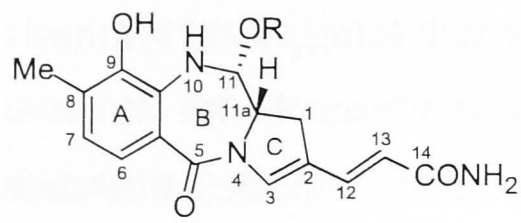
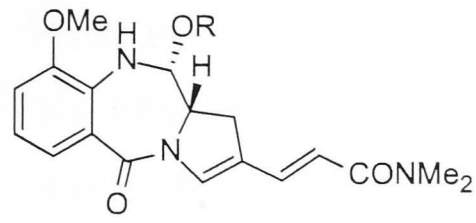
Abstract

The work detailed in this thesis describes the development of a suitable synthetic strategy for the synthesis of pyrrolo[2,1-*c*][1,4]benzodiazepine (PBD) natural products (**1-3**) – antitumour antibiotics which are capable of covalently binding to DNA and exhibit potent *in vitro* and *in vivo* cytotoxicity.



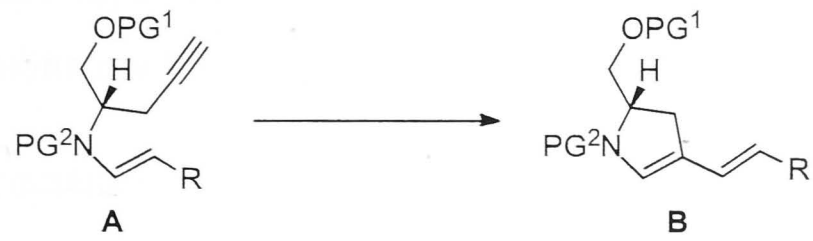
1a R=H (anthramycin)
1b R=Me (anthramycin methyl ether)



2a R=H (porothramycin A)
2b R=Me (porothramycin B)

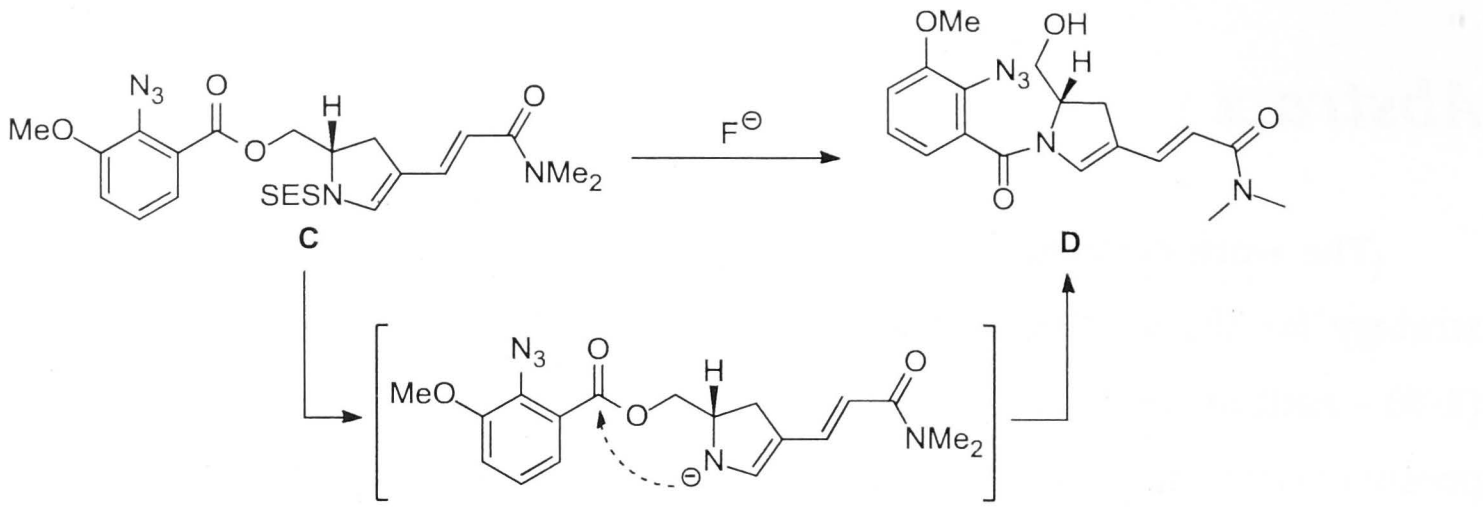
sibiromycin **3**

The synthetic sequence involved the introduction of the key stereocentre by asymmetric alkylation and construction of the C-ring dihydropyrrole moiety by ring-closing enyne metathesis (RCEYM). Studies into the metathesis rearrangement involved investigations into the employment of relay-ring closing metathesis (RRCM) on substrate **A** (R = CO_2Allyl) to aid delivery of the chosen catalyst. However, these attempts proved unsuccessful and the metathesis substrate was redesigned to include an allylic alcohol moiety (**A**; R = CH_2OH) which led to the successful metathesis rearrangement and delivered the dihydropyrrole moiety with an allylic alcohol side chain (**B**; R = CH_2OH).



Following the metathesis rearrangement, subsequent oxidation of the allylic alcohol moiety (**B**; R = CH_2OH) proved difficult and thus, was extensively investigated to provide a suitable protocol for the synthesis of the required dimethyl amide (**B**; R = $CONMe_2$) associated with porothramycin (**2**).

A brief investigation into appropriate nitrogen protecting groups led to the use of the 2-trimethylsilylethanesulfonyl (SES) protecting group. Unfortunately, there were problems related to the removal of the SES group from the dihydropyrrole **B** (PG^2 = SES; R = $CONMe_2$) and this led to the development of substrate **C** which successfully participated in an intramolecular substitution upon SES deprotection to give amide **D**. Studies into the conversion of this compound to the desired natural product by way of an oxidation and Staudinger reaction were also undertaken, however, results obtained could not conclusively determine that porothramycin (**2**) had been synthesised.



The sum of the efforts presented in this thesis, whilst not delivering a total synthesis of the target compound (**2**), does provide a suitable and feasible protocol with which to synthesise the target natural product (**2**) as well as other compounds in the same class (**1** & **3**).

Acknowledgements

First and foremost, I would like to thank my supervisor, Dr Malcolm McLeod, for his support and guidance throughout this degree. Thank you for always having the door open to provide me with and discuss ideas when problems arise and giving me the wonderful opportunity to partake my PhD at the Australian National University.

Secondly, I would like to thank the Australian National University for allowing me to study at the Research School of Chemistry and the provision of excellent services as overseen by staff in the RSC. In particular, I would like to thank Tony Herlt for his help and expertise in the use of the chiral HPLC and the mass spectrometry unit staff for their outstanding work in obtaining the desired spectra in a timely manner. I would also like to thank both the ANU and the RSC for the scholarships and funding provided to me.

It would not have been possible to do what I've been able to do without the support of the McLeod group – in particular Joey, Shane, Dwain, Luke and Masruri – for their invaluable insights into their fields of expertise and making the tough times more enjoyable. Thank you for the coffees at any time of the day, the impromptu lunch and dinner outings and your friendship through the years.

I would like to thank Andrew for supporting me through the highs and lows and encouraging me to better myself in my chosen field of study. Thank you for everything you've done and for making my life easier when times are tough.

To my family, especially my mum and dad, thank you for your unconditional support and keeping me grounded. While you may not have understood what it was I set out to do, you gave me the chance to do what I felt I wanted to do. I definitely would not have been able to do this without you.

To the rest of my friends, especially Rizsa, for our long coffees and chats and reminding me of His plan – whether in times of joy or through trials and tribulations. Thank you for the care and support you have all shown me through this time and sticking by me even when I go MIA.

Abbreviations

$[\alpha]_D$	specific rotation
°C	degrees Celsius
µmol	micromole(s)
^{13}C NMR	carbon nuclear magnetic resonance
18c6	18-crown-6
^{1}H NMR	proton nuclear magnetic resonance
Ac	acetyl
AcOH	acetic acid
app.	apparent
aq.	aqueous
Ar	aryl
Atm.	atmosphere
Bn	benzyl
Boc	*tert*-butyl carbamate
br	broad
ca.	approximately
calcd	calculated
CM	cross metathesis
cm	centimetre(s)
conc.	concentrated
CSA	camphorsulfonic acid
CT-DNA	calf thymus DNA
d	day(s)
d	doublet
DABCO	1,4-diazabicyclo[2.2.2]octane
DBU	1,8-diazabicyclo[5.4.0]undec-7-ene
DCE	dichloroethane
DCM	dichloromethane
DIBAL-H	diisobutylaluminium hydride
dil.	dilute
DIPEA	diisopropylethylamine (Hunig's base)
dm	decimetre(s)
DMAP	4-dimethylaminopyridine
DMF	*N,N*-dimethylformamide

DMP	Dess-Martin periodinane
DMSO	dimethylsulfoxide
DNA	deoxyribonucleic acid
ee	enantiomeric excess
equiv.	equivalents
ESI$^+$	electrospray ionisation
Et	ethyl
Et_3N	triethylamine
EtOH	ethanol
G-I	Grubbs' 1st generation catalyst
G-II	Grubbs' 2nd generation catalyst
h	hour(s)
HCl	hydrochloric acid
HG-I	Hoveyda-Grubbs 1st generation catalyst
HG-II	Hoveyda-Grubbs 2nd generation catalyst
HPLC	high performance liquid chromatography
HRMS	high resolution mass spectrometry
Hz	hertz
IC_{50}	inhibition constant
imid.	imidazole
in vivo	within the living
in vitro	within glass
IPA	isopropyl alcohol (isopropanol)
***i*Pr**	isopropyl
***i*PrOH**	isopropanol
IR	infrared
J	coupling constant
lit.	literature
M	molar
m	multiplet
m.p.	melting point
m/z	mass to charge ratio
Me	methyl
MeCN	acetonitrile
MeOH	methanol
MHz	megahertz
min	minute(s)
mL	millilitre(s)

mM	millimolar
mmol	millimole(s)
mol	mole(s)
MOM	methoxymethyl
MOMCl	chloromethyl methyl ether
MS	mass spectrometry
MsCl	methanesulfonyl chloride (mesyl chloride)
NMM	*N*-methylmorpholine
NMO	*N*-methylmorpholine *N*-oxide
NMR	nuclear magnetic resonance
***p*-**	para-
PBD	pyrrolo[2,1-*c*][1,4]benzodiazepine
PG	unspecified protecting group
Ph	phenyl
PhH	benzene
PhMe	toluene
PMB	*p*-methoxybenzyl
PTC	phase transfer catalyst
pyr.	pyridine
q	quartet
R	unspecified group
Raney-Ni	Raney nickel
RCEYM	ring closing enyne metathesis
RCM	ring closing metathesis
R_f	thin layer chromatography retardation factor
RRCM	relay-ring closing metathesis
rt	room temperature
s	singlet
SAR	structure activity relationship
SES	2-trimethylsilylethanesulfonyl
SESCl	2-trimethylsilylethanesulfonyl chloride
t	triplet
TASF	tris(dimethylamino)sulfonium difluorotrimethylsilicate
TBAF	tetrabutylammonium fluoride
TBDPS	*tert*-butyldiphenylsilyl
TBS	*tert*-butyldimethylsilyl
TBSCl	*tert*-butyldimethylsilyl chloride
Temp.	temperature

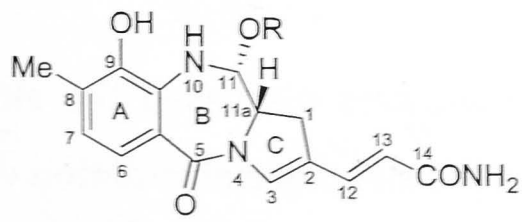
Tf	triflyl
TFA	trifluoroacetic acid
THF	tetrahydrofuran
tlc	thin layer chromatography
T_m	melting temperature
TMS	trimethylsilyl
TMSCl	chlorotrimethylsilane (or trimethylsilyl chloride)
TPAP	tetra-*n*-propylammonium perrutherate
Ts	*p*-toluenesulfonyl (tosyl)
TsCl	*p*-toluenesulfonyl chloride (tosyl chloride)
UV	ultraviolet
w/v	unit weight per unit volume (%)
δ	chemical shift (parts per million)
ν_{max}	infrared absorption max

Table of Contents

Chapter 1 Introduction

Small molecules with the ability to interact in a sequence specific manner with DNA have created great interest and potential for the design of novel chemotherapeutic agents or small molecules for gene recognition and regulation.

Pyrrolo[2,1-*c*][1,4]benzodiazepines (PBDs), also known as the "anthramycins", are produced by various *Streptomyces* species (Figure 1.1).[1] These antitumour antibiotics are capable of covalently binding to DNA through the formation of an aminal linkage between the exocyclic amine in guanine and the C11 carbinolamine present in compounds **1-3** or the imine as observed in compound **4**.[2] They have also been shown to display potent *in vitro* and *in vivo* cytotoxicity which is attributed to their ability to disrupt endonuclease activity and inhibit DNA transcription.[3] Their ability to bind to DNA lies in the ever present 11a-(*S*) absolute configuration – giving these molecules the essential twist to allow them to fit into, and interact with, the minor groove.[4,5]



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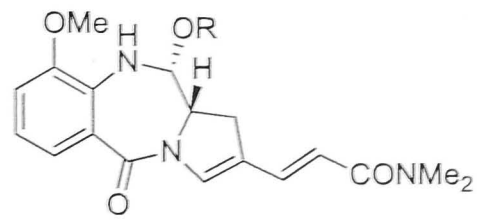

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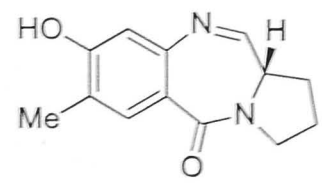
sibiromycin **3**



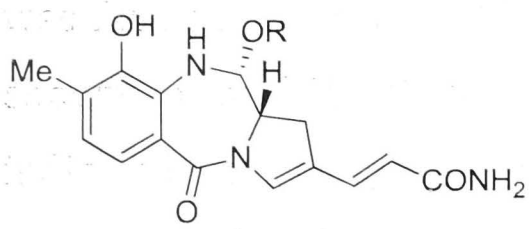
DC-81 **4**

Figure 1.1 *– Examples of pyrrolo[2,1-c][1,4]benzodiazepines*

1.1 Anthramycin

Anthramycin (**1**), the PBD that gives rise to the name for this class of compounds, was first observed in 1963 by Tendler and Korman in a fermentation broth which was shown to exhibit antibiotic properties and *in vivo* antitumour activity.[6] Initial studies indicated activity against several gram-positive strains of bacteria and inhibition of sarcoma and adenocarcinoma tumours but no activity against gram-negative bacteria and leukemia.[6] The presence of both antibiotic and antitumour properties gives rise to the classification of anthramycin as an antitumour antibiotic.

In 1965, anthramycin (**1**) was isolated and characterised by Leimgruber and co-workers.[7] The methods used in the isolation of anthramycin led to 3 forms – the hemiaminal-bearing anthramycin (**1a**), the more stable anthramycin methyl ether (**1b**), and the dehydro congener – anhydroanthramycin (**5**) (Figure 1.2). At the same time, Leimgruber also reported the isolation and characterisation of a minor fermentation product, which was dubbed the "yellow pigment" **6** and later determined to be desdihydroxydesmethylanthramycin (Figure 1.2).[7]



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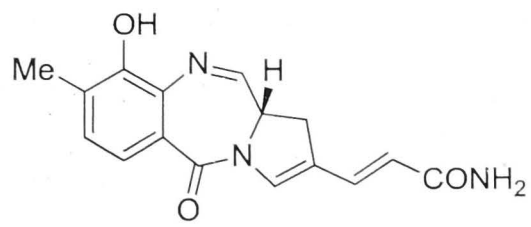
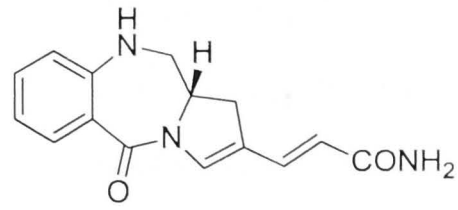


anhydroanthramycin **5**



"yellow pigment" **6**
desdihydroxydesmethylanthramycin

Figure 1.2 *– Compounds identified in fermentation broth of Streptomyces refuineus* var. *thermotolerans*[7]

A further report by Leimgruber and co-workers discussed the elucidation of the structure of anthramycin (**1**) and indicated that the structure elucidation was aided by the investigation of the "yellow pigment" **6**.[8]

The structure of compound **6** was determined using NMR, other spectroscopic studies, such as IR and UV, and analysis of products obtained from chemical transformations of the original molecule. The (*E*)-configured double bond on the side chain was assigned based on the coupling constant (J = 15 Hz) between the respective protons present at C12 and C13, and the conjugated primary amide was identified by a transformation to, and identification of, the conjugated nitrile.[8] With this data gathered from compound **6**, Leimberger proposed a tricyclic structure **6** which allowed for all heteroatoms (with the empirical formula $C_{15}H_{15}N_2O_2$ as determined by HRMS) and functional groups identified.[7]

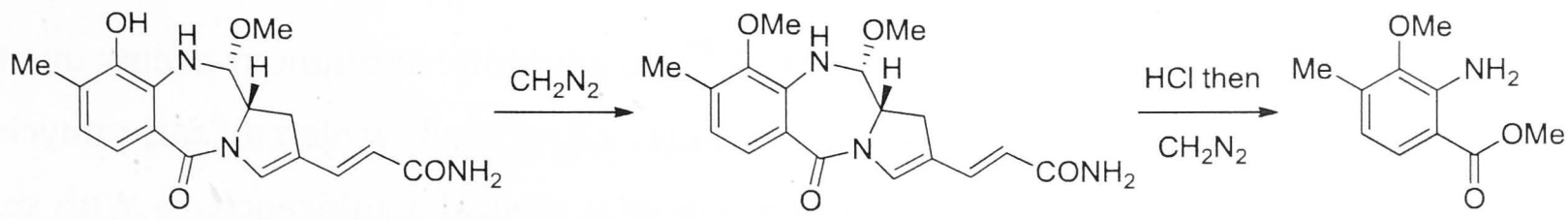
There were two possible parent tricyclic structures; the first being a pyrrolobenzodiazepine core **7**, and the second being a pyridoquinazoline core **8**. The comparison of spectroscopic properties (UV, IR and NMR) between the parent **7** and the tetrahydropyrrole derivative of the 'yellow pigment' **6** were very similar, indicating the presence of a pyrrolobenzodiazepine core. This was also supported by the observation of fragments attributed to the indicated fragmentation a/b (Figure 1.3) in the mass spectrum of compound **6** and other transformation products.[8]

pyrrolobenzodiazepine core **7** pyridoquinazoline core **8**

Figure 1.3 *– Two possible tricyclic cores (**7** and **8**) identified for "yellow pigment" **6**[8]*

Having elucidated the structure of the 'yellow pigment' **6**, Leimgruber and co-workers turned their attention to anthramycin methyl ether (**1b**).[8] A comparison of spectroscopic data obtained from compounds **6** and **1b** showed many common features and after further examination of NMR data, Leimgruber proposed the structure **1b**. The structure was confirmed through several transformations of anthramycin methyl ether (**1b**) with main studies concerning the structure of the A-ring and the configuration of the C11 stereocentre.

The A-ring was confirmed by firstly forming the phenolic ether **9**, then hydrolysis and esterification to give methyl 3-methoxy-4-methyl-anthranilate (**10**) which was identical by comparison with an authentic sample (Scheme 1.1).



anthramycin methyl ether **1b** **9** **10**

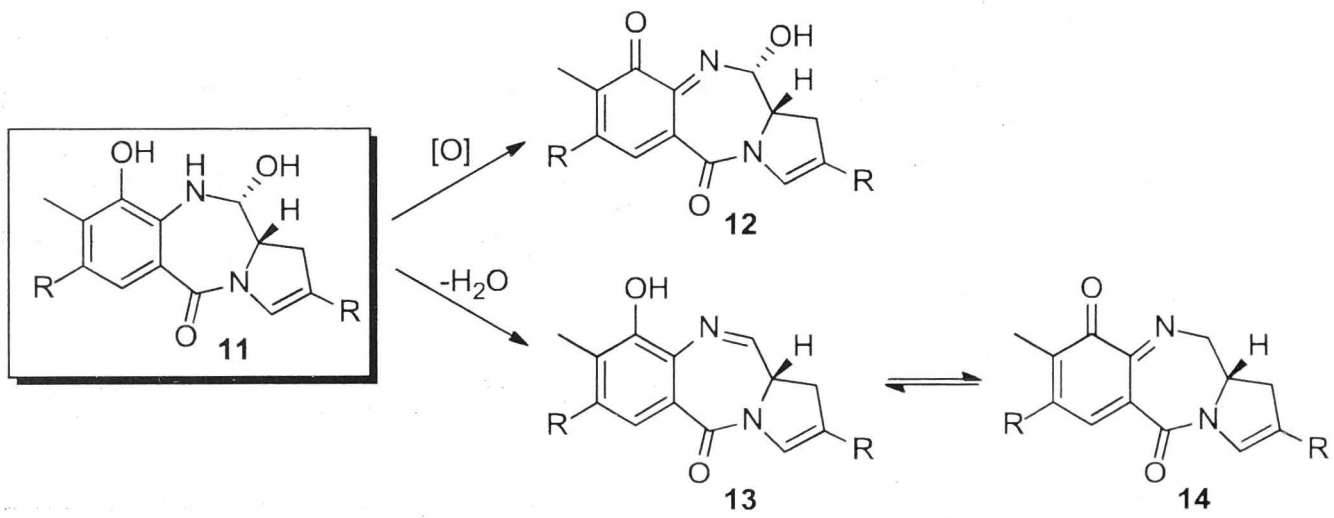
Scheme 1.1 *– Fragments obtained from hydrolysis of anthramycin methyl ether (**1b**)*

The relative configuration of the C11 and C11a stereocentres were confirmed by the absence of coupling between the two respective protons indicating a dihedral angle of 90°, whereas in the C11-epimer of anthramycin (**1**), coupling is observed between the C11 and C11a protons. The dihedral angle of 90° was also confirmed by an inspection of Dreiding models.

The assignment of the absolute stereochemistry as 11-(*R*) and 11a-(*S*) was determined by Leimgruber and co-workers in their total synthesis of anthramycin (**1**), which is discussed later in this chapter.[9]

1.1.1 Pyrrolo[2,1-*c*][1,4]benzodiazepines in clinical trials

As a new and upcoming antibiotic antitumour drug in the 1960s, anthramycin (**1**) and others of the same class were subjected to clinical trials.[10] PBDs were observed to be most effective for gastrointenstinal and breast tumours as well as lymphomas and sarcomas, however, the clinical studies were limited due to observations of cardiotoxicity and acute tissue necrosis at the site of injection.[11] It had been thought that cardiotixicty could arise from the formation of *ortho*-quinone imine products, such as compounds **12** and **14** – which are known to be cardiotoxic (Scheme 1.2).[12]



Scheme 1.2 *– Oxidation/tautomerisation of PBDs to* ortho*-quinone imines*

1.1.2 Structure activity relationship of pyrrolo[2,1-*c*][1,4]benzodiazepines

Although there are downsides to using PBDs as antibiotic antitumour agents due to their side effects, there are still countless variations of naturally isolated "anthramycin-type" PBDs and their analogues which show potential clinical significance.[1,12] With this knowledge and new PBDs continually being isolated, it is difficult to discount their biological activity and rule them out as candidates in the search for new antitumour agents.[12-14]

Through the years, studies and reviews of PBDs, especially in the field of medicinal chemistry, have identified them as scaffolds for the design and synthesis of anti-tumour drugs and have highlighted the versatility of these small molecules as well as their high cytotoxicity.[15,16] However, as with all drugs, in addition to cytotoxicity, detrimental effects to the host must also be taken into account.

PBDs generally have varying substitutions on the A-ring and C-ring as well as differing degrees of saturation on and around the C-ring. Due to the great number of variations which may be imposed on the general PBD core, structure activity relationship studies have been undertaken to determine the influence of various substitutions on DNA binding and their biological activities.[15]

A review by Hurley and Thurston[15] in 1984 provided the first SAR study of the anthramycins. Through the use of space-filling models, they presented a detailed summary of predicted structure activity relationships displayed in Figure 1.4. These results reassert the importance of the carbinolamine and 11a-(*S*) stereocentre present in the anthramycins which give them their inherent ability to bind to DNA. The rest of the structure may accommodate a wide range of substituents however, small or narrow substituents are preferred. In reference to the hydroxyl groups on the A-ring, the presence of such groups at either C7 or C9 were predicted to cause cardiotoxicity by way of *ortho*-quinone formation – a side effect observed during clinical trials.[10,11]

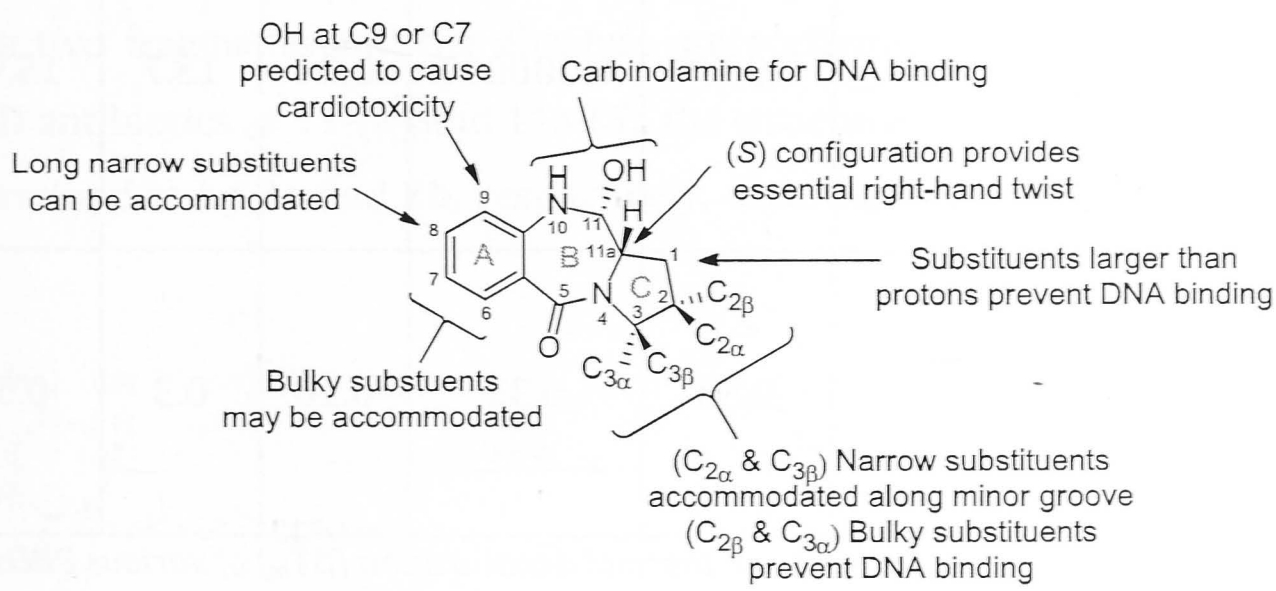


Figure 1.4 *– Pyrrolo[2,1-c][1,4]benzodiazepine nucleus showing predicted structure activity relationships*[15]

A decade later, after extensive studies on the binding of PBDs to DNA,[5,17-20] Thurston and co-workers[21] investigated the effect of A-ring modifications on the binding behaviour and cytotoxicity of PBDs. The study was based on DC-81 (**4**), which carries a saturated and unsubstituted C-ring. At the conclusion of this study, although it was found that electron donating substituents, such as OH or OMe, exhibited greater binding affinity, the presence of an unsaturated substituted C-ring had a much greater influence on DNA binding and cytotoxicity (Table 1.1).[21]

The thermal denaturation studies (Table 1.1), which determined the melting stabilisation (ΔT_m) of double-stranded calf thymus DNA (CT-DNA) following incubation with various PBDs at 37 °C, indicated that unsaturated C-ring compounds, such as anthramycin methyl ether (**1b**) and sibiromycin (**3**), had the highest DNA-binding affinity

as they produced the largest ΔT_m shifts.[21] These unsaturated compounds were also found to have the highest cytotoxicity when examined against three cell lines (L1210 leukemia, ADJ/PC6 plasmacytoma & CH1 human ovarian) with IC_{50} values ranging from 0.000017-0.32 μM. The saturated C-ring compounds such as DC-81 (**4**) were observed to have much smaller ΔT_m shifts and higher IC_{50} values.

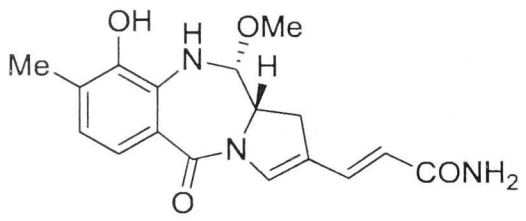
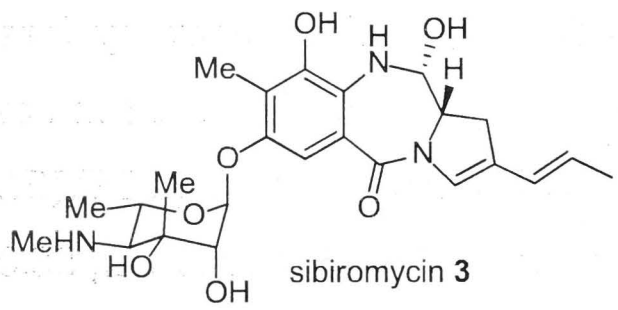
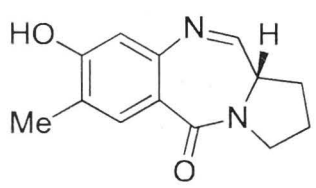
Compound	Cytotoxicity (IC_{50} μM)*			ΔT_m (°C)† after incubation for:		
	L1210	ADJ/PC6	CH1	0 h	4 h	18 h
 anthramycin methyl ether **1b**	0.022	0.0028	0.32	9.4	11.2	13.0
 sibiromycin **3**	0.0029	0.000017	0.04	15.7	15.9	16.3
 DC-81 **4**	0.38	0.33	0.10	0.3	0.5	0.7

Table 1.1 *– Cytotoxicity (IC_{50}) and thermal denaturation (ΔT_m) of various PBDs*

**Dose of PBD required to inhibit cell growth by 50% compared to PBD-free controls †Thermal denaturation studies with CT-DNA (incubation at 37 °C)[21]*

The results obtained from the SAR study suggested that the flattening of the C-ring caused by C-ring unsaturation led to a better fit into the minor groove of DNA and hence, higher DNA-binding affinity and higher cytotoxicity. These conclusions were also confirmed during a further study into the effect of unsaturation on the cytotoxicity and DNA-binding reactivity of PBDs.[22]

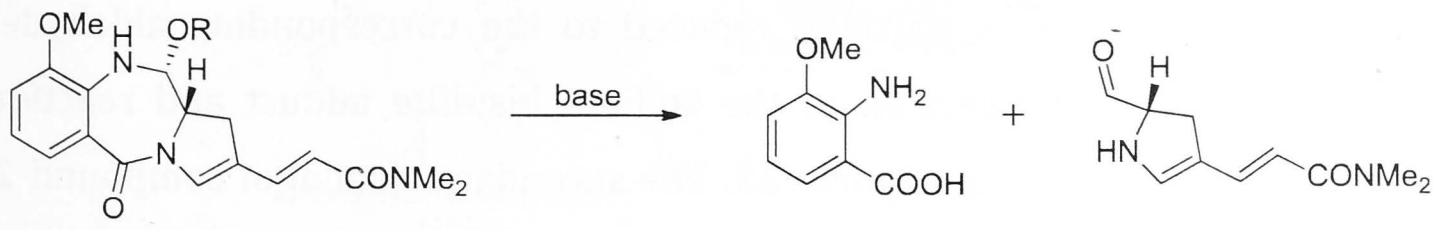
The observations gathered from the various structure activity relationship studies point towards porothramycin (**2**) – with no hydroxyl group in the C9 position, an unsaturated and substituted C-ring, and a single electron donating group on the A-ring – as a good starting point for the synthesis of potent antitumour drugs.

1.2 Porothramycin

Porothramycin (**2**) was first isolated from *Streptomyces albus* by Tsunakawa and co-workers in 1987 in both the natural hydroxyl form [porothramycin A (**2a**)] and the methyl ether form [porothramycin B (**2b**)] – present when isolated or purified using methanol.[23] Both forms of natural product **2** have been shown to display antibacterial and potent antitumour properties.

The analysis of physio-chemical and biological properties of the porothramycins indicated a resemblance to the anthramycins. They did, however, have a distinct structural difference when analysed by ^{1}H NMR spectroscopy as the presence of three contiguous aromatic protons was a first among the group of known PBDs.[23]

Further analysis of the porothramycins by base hydrolysis produced two UV-absorbing compounds, which were determined to be the 1,2,3-trisubstituted aromatic compound **15** and 2-formyldihydropyrrole-4-*N,N*-dimethylacrylamide (**16**) (Scheme 1.3). With these two fragments and the absolute stereochemistry assigned by analogy with known PBD antibiotics as 11-(*R*) and 11a-(*S*), the structure of the porothramycins A and B were determined to be **2a** and **2b**, respectively, differing only by the functional group at C11.[23]



2a R=H (porothramycin A)
2b R=Me (porothramycin B)

15 **16**

Scheme 1.3 *– Analysis of porothramycin (**2**) by base hydrolysis*

The interesting structure and biological activity of porothramycin (**2**) presents this small molecule as a good target for natural product synthesis towards an antitumour drug and a stepping stone for the synthesis of other natural PBDs and analogues.

1.3 Syntheses of pyrrolo[2,1-*c*][1,4]benzodiazepines

Being biologically significant and bearing synthetically interesting moieties, the PBDs present themselves as desirable targets in the field of synthetic organic chemistry. As such, there have been several syntheses of both anthramycin (**1**) and porothramycin (**2**) reported to date and a summary of each synthesis will be presented herein.

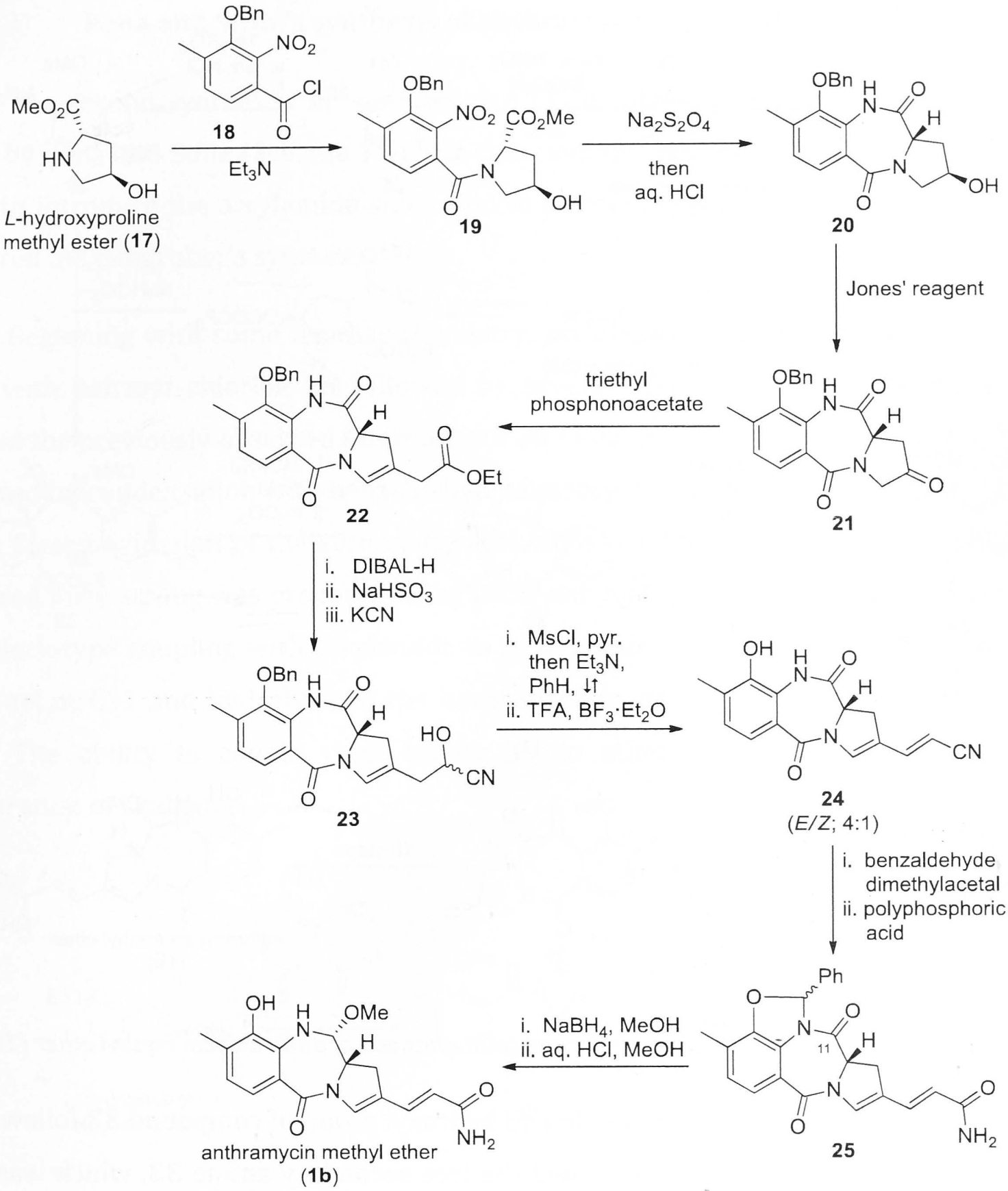
1.3.1 Previous total syntheses of anthramycin

1.3.1.1 Leimgruber synthesis of anthramycin

In 1968, following the structure elucidation and characterisation of anthramycin (**1**) in 1965, Leimgruber and co-workers reported the first total synthesis of this natural product, and by doing so confirmed its unique structure.[7-9]

The synthesis (Scheme 1.4) began with the acylation of *L*-hydroxyproline methyl ester (**17**) with the desired benzoyl chloride **18** to give amide **19**, which was subsequently reduced with sodium dithionite and cyclised in the presence of acid to form lactam **20**. Manipulation of the C-ring began with the oxidation of the secondary alcohol to the corresponding ketone **21** using Jones' reagent and a Horner-Wadsworth-Emmons reaction with the sodium salt of triethyl phosphonoacetate to yield dihydropyrrole **22**. The ester moiety of compound **22** was partially reduced to the corresponding aldehyde using DIBAL-H, followed by a conversion to the sodium bisulfite adduct and reaction with potassium cyanide to form cyanohydrin **23**. The secondary alcohol of compound **23** was dehydrated through a mesylation and elimination reaction sequence to provide the corresponding vinyl nitrile, which was subsequently debenzylated to form phenolic nitrile **24**. The desired (*E*)-isomer of conjugated nitrile **24** was condensed with benzaldehyde dimethyl acetal and then hydrolysed using polyphosphoric acid to form the desired benzoxazoline amide **25**. The carbonyl group at C11 was reduced using sodium borohydride in methanol, and the benzoxazoline functionality was hydrolysed under acidic conditions in methanol to yield anthramycin methyl ether (**1b**) (2.6% over 15 steps).[9]

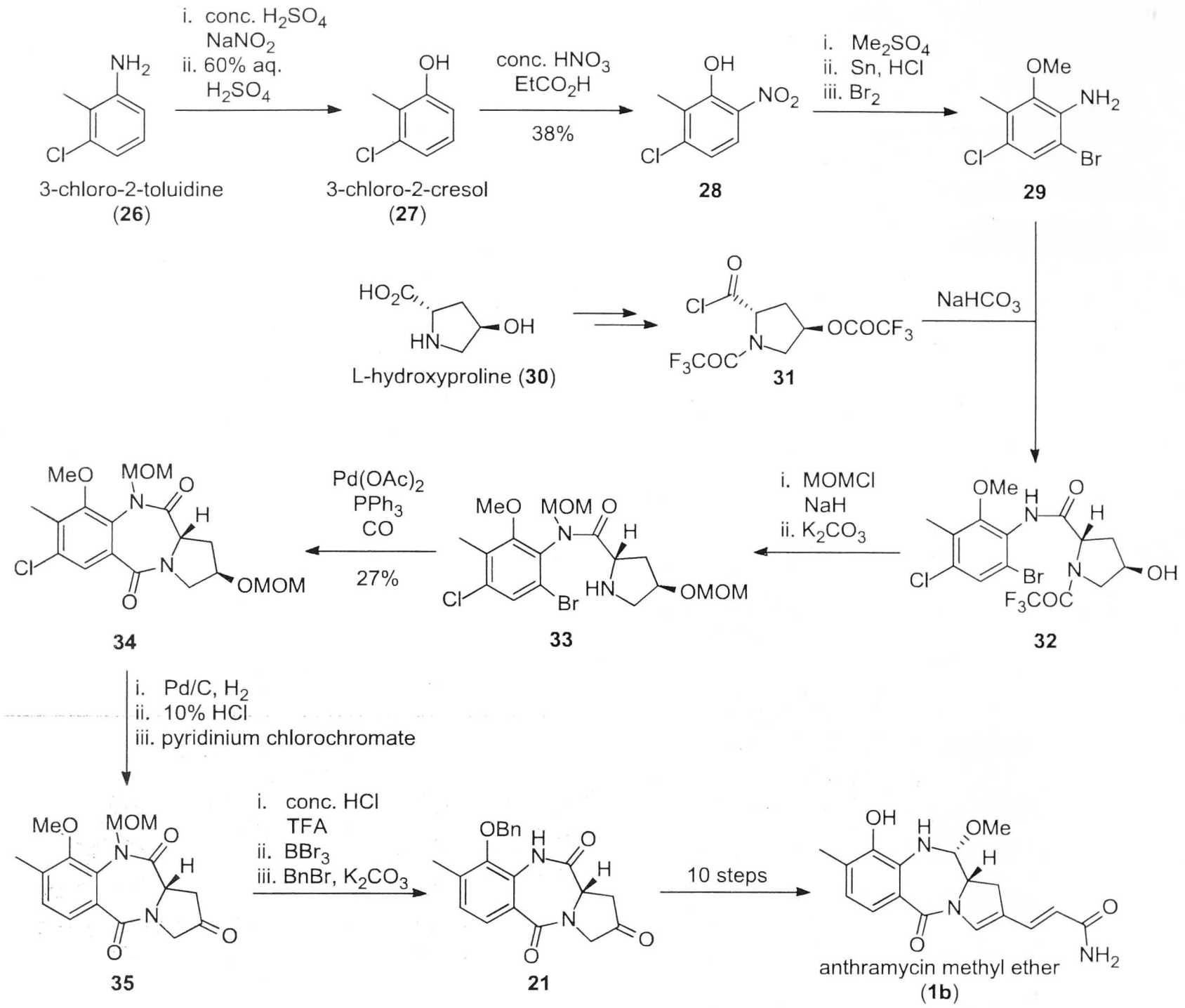
In the years following Leimgruber's total synthesis of anthramycin,[9] there were a number of investigations into the synthesis of the pyrrolobenzodiazepine core, however, a new total synthesis of this PBD wasn't published until the 1980s.[24,25] The development of palladium-catalysed chemistry in the 1970s led to the employment of such chemistry in the total synthesis of natural products and the two syntheses of anthramycin following this period both involved palladium.[26]



Scheme 1.4 *– Leimgruber and co-workers' synthesis of anthramycin methyl ether (**1b**)*[9]

1.3.1.2 Ishikura synthesis of anthramycin

The first, a formal total synthesis of anthramycin (**1**) by Ishikura (Scheme 1.5), utilised a palladium-catalysed carbonylation procedure previously developed in the group to close the B-ring and form the desired tricyclic structure.[27-29] Beginning with the synthesis of an A-ring carrying the desired handle for the carbonylation procedure, 3-chloro-2-toluidine (**26**) was converted to 3-chloro-2-cresol (**27**), which was then nitrated to give both the undesired 4-nitro and desired 6-nitro chlorocresol **28** in a 1:1 ratio. With compound **28** in hand, methylation of the phenol, followed by a tin reduction and bromination afforded the desired 3-toluidine **29**, which was then coupled to a *L*-hydroxyproline derivative **31** to produce amide **32**.



Scheme 1.5 *– Ishikura and co-workers' formal total synthesis of anthramycin methyl ether (**1b**)*[27]

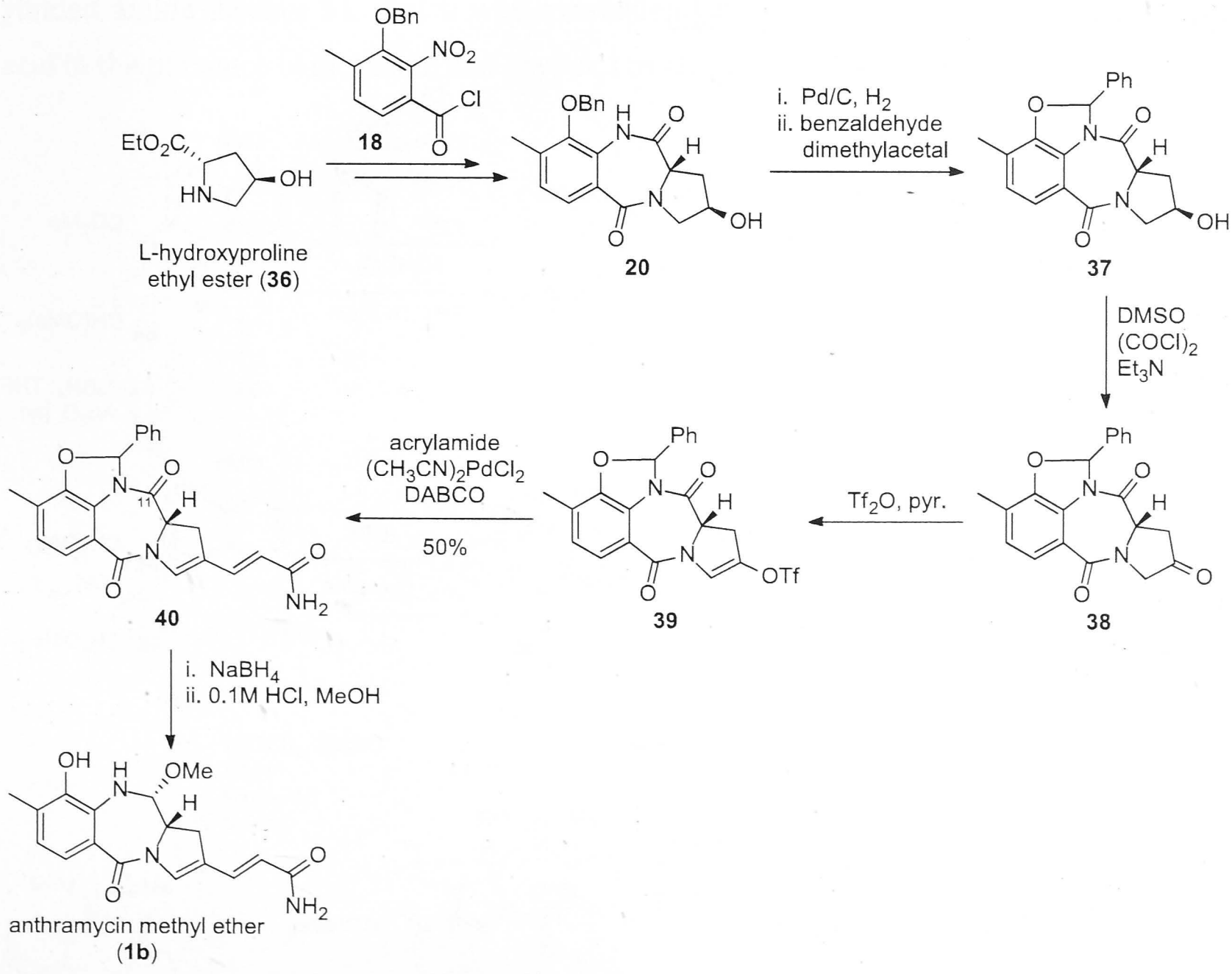
Protection of the secondary amide and hydroxyl group of compound **32** followed by removal of the trifluoroacetamide yielded the free secondary amine **33**, which was now ready to undergo carbonylation. A palladium-catalysed carbonylation then produced the desired diazepinone derivative **34**, albeit in 27% yield. Having successfully constructed dilactam **34**, dechlorination, selective MOM deprotection and oxidation of the secondary alcohol yielded ketone **35**, which was then globally deprotected and *O*-benzylated to produce **21**, an intermediate previously prepared in the Leimgruber synthesis of anthramycin methyl ether (**1b**).[9]

Although the key step of palladium-catalysed carbonylation was not very efficient, the Ishikura formal synthesis of anthramycin demonstrated that palladium catalysed coupling reactions were a viable route for the synthesis of the PBD core.[27,29]

1.3.1.3 Pena and Stille's synthesis of anthramycin

The second synthesis of anthramycin (**1**) involving palladium was published in 1989 by Pena and Stille (Scheme 1.6).[30] In this case, the palladium catalysed reaction was used to introduce the acrylamide side chain in a more efficient manner than the 8 steps required in Leimgruber's synthesis.[9,30]

Beginning with some familiar chemistry, acylation of *L*-hydroxyproline ethyl ester (**36**) with benzoyl chloride **18** followed by several functional group interconversions yielded the previously observed intermediate **20**.[9] Removal of the benzyl protecting group followed by condensation with benzaldehyde dimethyl acetal produced benzoxazoline **37**, and a Swern oxidation of the secondary alcohol yielded ketone **38**. The vinyl triflate **39** required for coupling was prepared using triflic anhydride in pyridine which participated in a Heck-type coupling with acrylamide to form amide **40**. Once again, reduction of the carbonyl at C11 and hydrolysis of the benzoxazoline yielded anthramycin methyl ether (**1b**). The ability to couple vinyl triflate **39** to other partners also allows for the preparation of analogues.



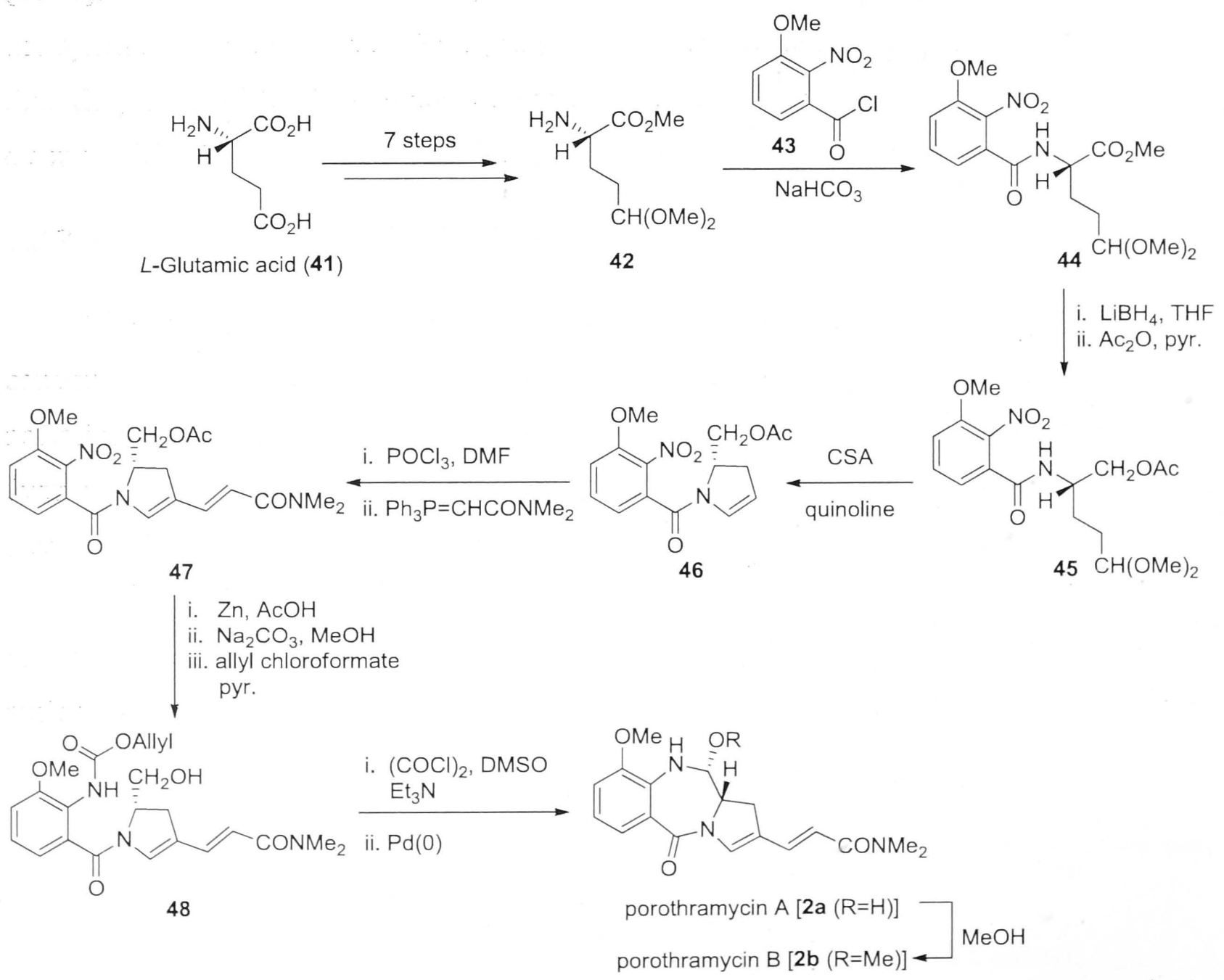
Scheme 1.6 – *Pena and Stille's total synthesis of anthramycin methyl ether (**1b**)*[30]

1.3.2 Previous syntheses of porothramycin

The stereoselective synthesis of (+)-porothramycin [(+)-**2**] has previously been completed three times – by Fukuyama and co-workers (1993),[31] Langlois and co-workers (1993),[32] and more recently by Vanderwal and co-workers in 2010.[33] It may be noted that the syntheses put forward by Fukuyama and Langlois bear very similar disconnections in that they involve the elongation of the side chain *via* an olefination reaction and the closure of the B-ring through the addition of an aniline moiety to an aldehyde.

1.3.2.1 Fukuyama synthesis of porothramycin

The synthetic strategy described by Fukuyama (Scheme 1.7) began with the conversion *L*-glutamic acid (**41**) to amino ester **42**.[31] The A-ring was introduced by acylation of amino acid derivative **42** with 3-methoxy-2-nitrobenzoyl chloride (**43**) to form amido ester **44**, which was subsequently reduced and acetylated to produce amido alcohol **45**. A cyclisation-elimination reaction of compound **45** with quinolinium camphorsulfonate delivered the C-ring in enamide **46**, which was formylated and olefinated under Vilsmeier-Haack and Wittig conditions, respectively, to form conjugated amide **47** bearing the required side chain.

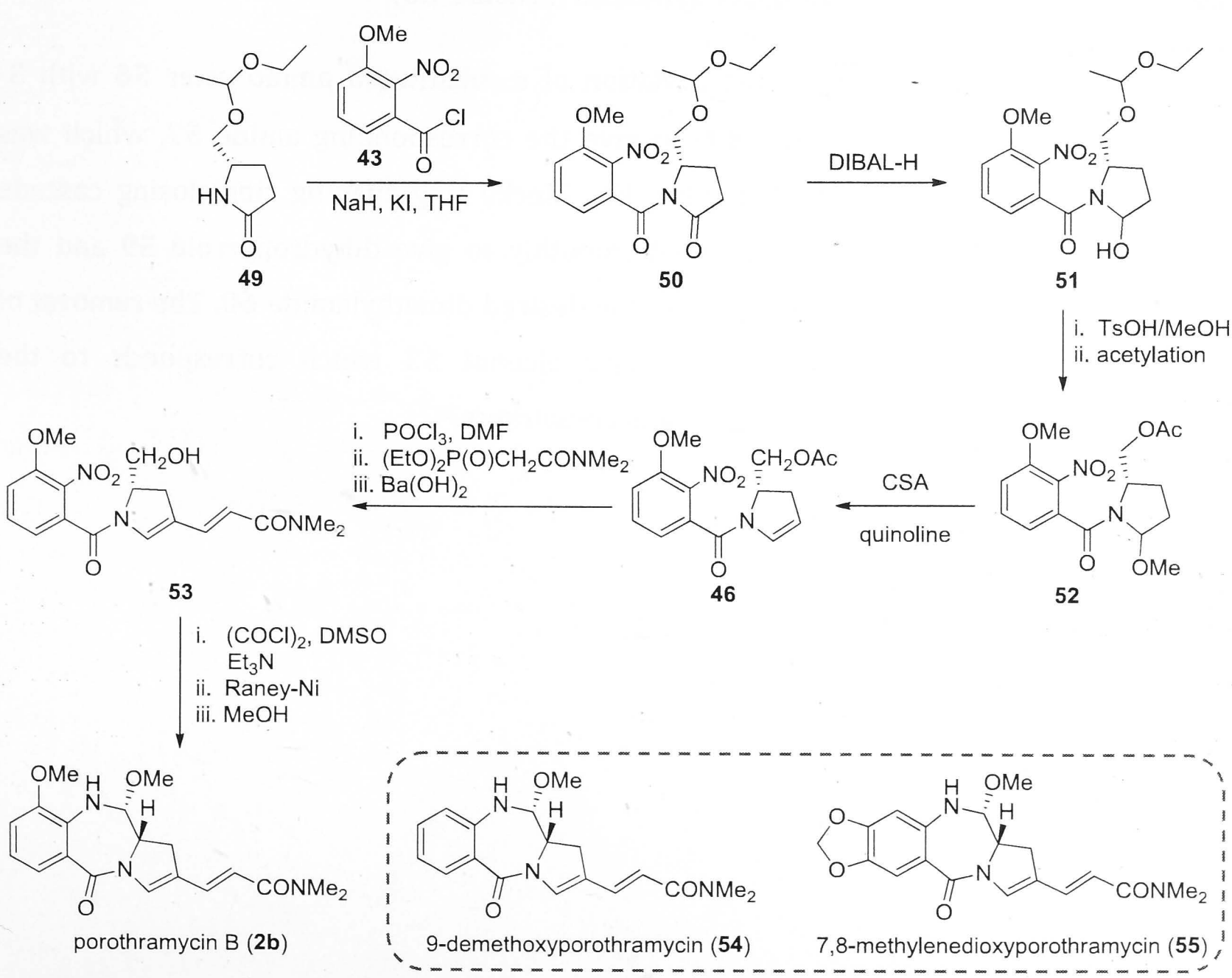


Scheme 1.7 *– Fukuyama total synthesis of (+)-porothramycin B [(+)-**2b**][31]*

Reduction of the nitro group to the aniline derivative followed by a deacetylation and acylation with allyl chloroformate afforded carbamate **48**. Oxidation of the primary alcohol under Swern conditions inititated a spontaneous intramolecular nucleophilic addition to establish the B-ring as a single stereoisomer, while the amine was liberated by way of a palladium-catalysed deprotection to afford porothramycin A (**2a**). However, due to instability of hemiaminal **2a**, it was converted to the methyl ether **2b** by crystallisation in methanol. This was the first total synthesis of porothramycin (**2**) and yielded the target **2a** in 9.2% in 18 steps.

1.3.2.2 Langlois synthesis of porothramycin

In light of the Fukuyama synthesis, Langlois and co-workers published their synthesis of (+)-porothramycin [(+)-**2**] (Scheme 1.8) which makes use of previously established chemistry used to form other natural PBDs.[9,31,34,35] Pyrrolidone **49** was acylated with 3-methoxy-2-nitrobenzoyl chloride (**43**) to introduce the A-ring and form imide **50**. A regioselective reduction of the pyrrolidone carbonyl group of compound **50** yielded amido alcohol **51**, which was consequently deprotected using *p*-toluenesulfonic acid in the presence of methanol and acylated to afford the methyl ether carbinolamide **52**.



Scheme 1.8 – *Langlois total synthesis of (+)-porothramycin B [(+)-**2b**][32]*

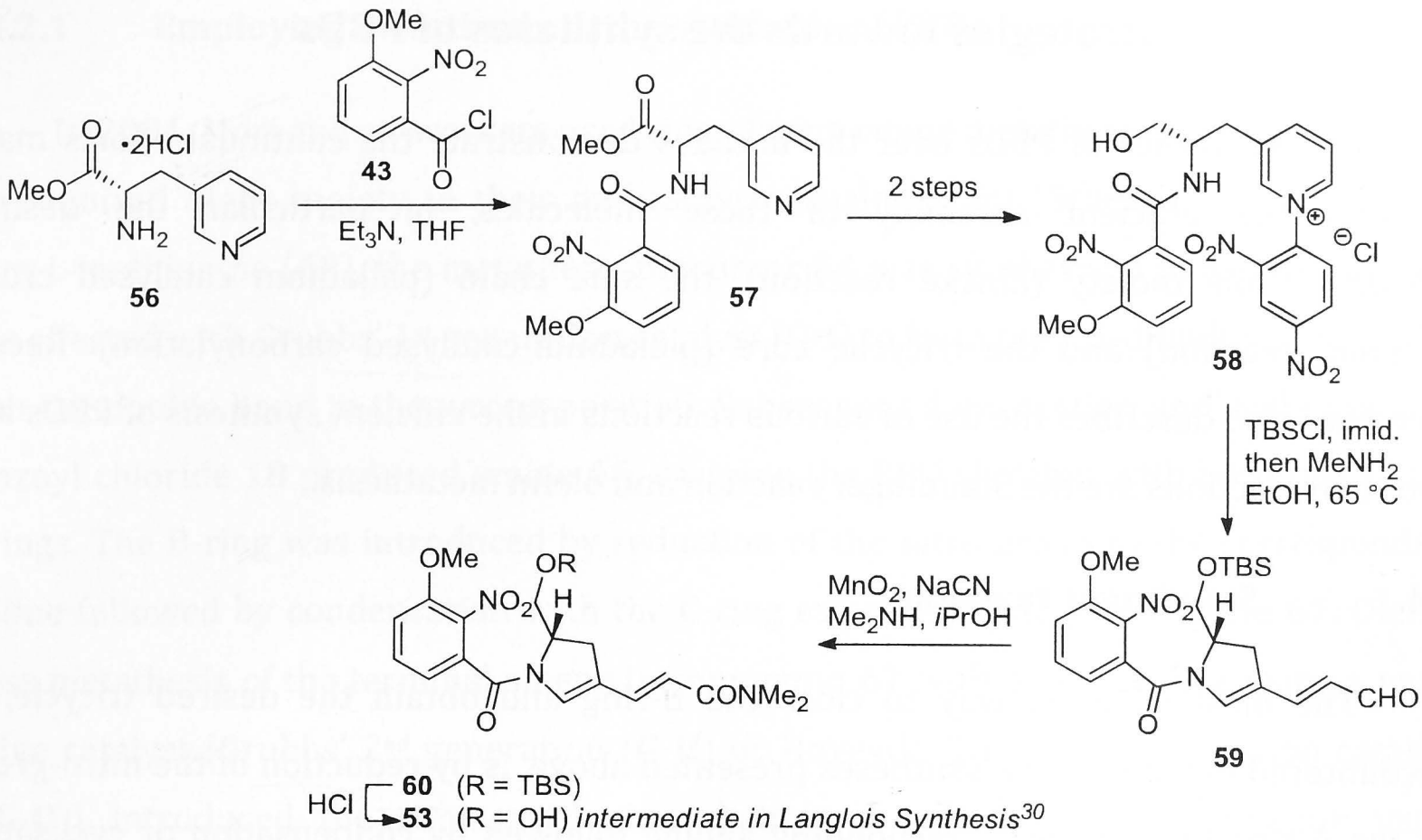
Elimination of the methyl ether functionality in compound **53** with quinolinium camphorsulfonate produced enamide **46**, an intermediate previously observed in the Fukuyama synthesis.[31] Once again, a formyl group was introduced using the Vilsmeier-Haack reaction, however, in this synthesis, the amide side-chain was delivered by a Horner-Wadsworth-Emmons reaction to give the desired dimethylamide **53**. The end game of the synthesis involved deacetylation and oxidation of the primary alcohol followed by reduction of the nitro group to the corresponding aniline which led to a spontaneous cyclisation. The cyclised product, presumably porothramycin A (**2a**), was not isolated but directly treated with methanol to produce porothramycin B (**2b**) in 13% yield over 11 steps.

Using the above-mentioned synthetic sequence, Langlois and co-workers have also prepared several porothramycin analogues, such as **54** and **55** (Scheme 1.8).[32,36]

1.3.2.3 Vanderwal synthesis of porothramycin

The most recent reported synthesis of (+)-porothramycin [(+)-**2**] published by Vanderwal and co-workers in 2010 (Scheme 1.9) involved the synthesis of the advanced intermediate **53** observed in Langlois' synthesis (Scheme 1.8).[33]

The synthesis began with the acylation of α-substituted amino ester **56** with 3-methoxy-2-nitrobenzoyl chloride (**43**) to give the corresponding amide **57**, which was converted into the precursor **58** for the key Zincke ring-opening ring-closing cascade reaction. The Zincke reaction proceeded smoothly to give dihydropyrrole **59** and the aldehyde thus formed was converted into the desired dimethylamide **60**. The removal of the TBS ether then provided the primary alcohol **53** which corresponds to the intermediate as synthesised by Langlois and co-workers.[33]



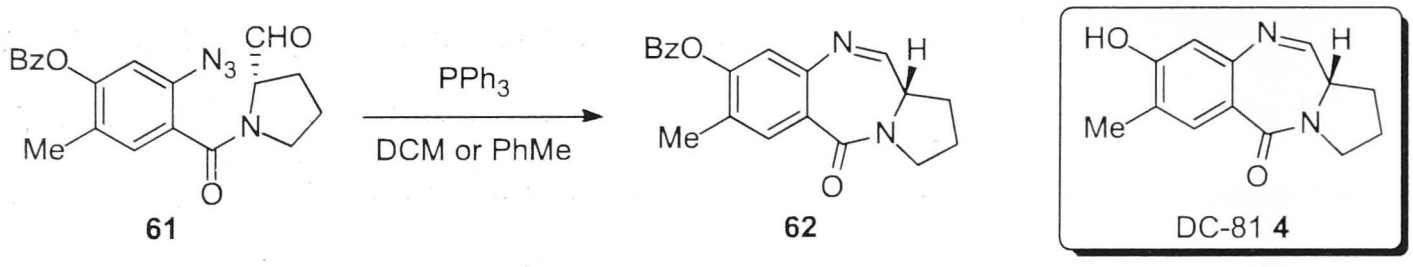
Scheme 1.9 – *Vanderwal formal synthesis of (+)-porothramycin A [(+)-**2a**] and B [(+)-**2b**][33]*

1.4 New strategies towards the syntheses of PBDs

The syntheses of PBDs over the decades demonstrate the continual efforts made towards the efficient assembly of these molecules, in particular the desired dihydropyrrole moiety (Zincke reaction), the side chain (palladium catalysed cross-coupling reaction) and the tricyclic core (palladium-catalysed carbonylation). Recent literature also describes the use of various reactions in the efficient synthesis of PBDs and two such reactions are the Staudinger reaction and olefin metathesis.

1.4.1 Staudinger reaction

The most common way to close the B-ring and obtain the desired tricycle, as encountered in many of the syntheses presented above, is by reduction of the nitro-group on the A-ring to give the corresponding aniline followed by condensation or cyclisation with a carbonyl functional group attached to the C-ring. In 1995, Eguchi and co-workers and Molina and co-workers successfully employed the Staudinger reaction, a reaction involving the coupling of azide **61** to the aldehyde functionality present in the C-ring to establish the tricyclic imine **62** en route to their syntheses of DC-81 (**4**) (Scheme 1.10).[37,38]



Scheme 1.10 *– Staudinger reaction to form B-ring of DC-81 (**4**)*[37,38]

1.4.2 Olefin metathesis

Olefin metathesis is a versatile reaction with a broad substrate tolerance and can be performed on dienes, enynes, and diynes. Careful catalyst selection (Figure 1.5) may allow for a variety of reactivities and substrate tolerance, as well as stereo- and regio-selectivity.[39] It is the development of enyne metathesis, which has been used extensively to install semi-cyclic dienes similar to that observed in the C-ring of PBDs, such as anthramycin (**1**), that has seen its use in the synthesis of this class of compounds.

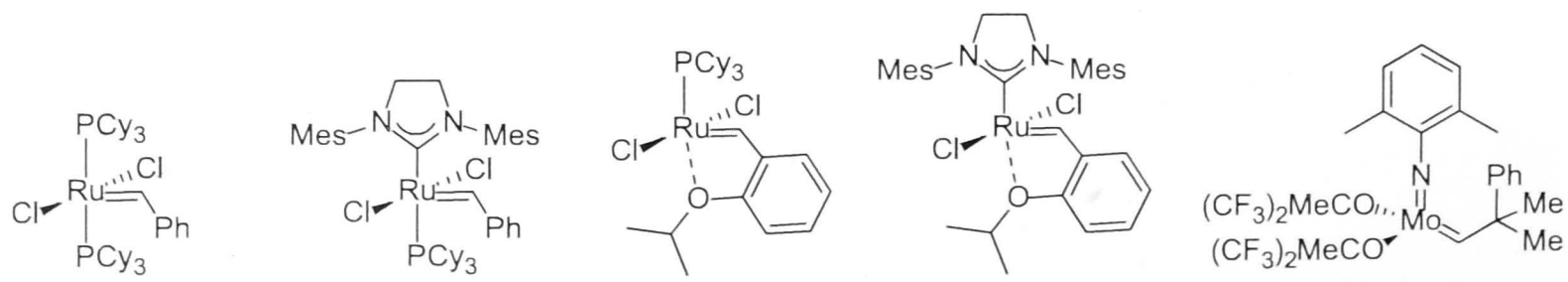
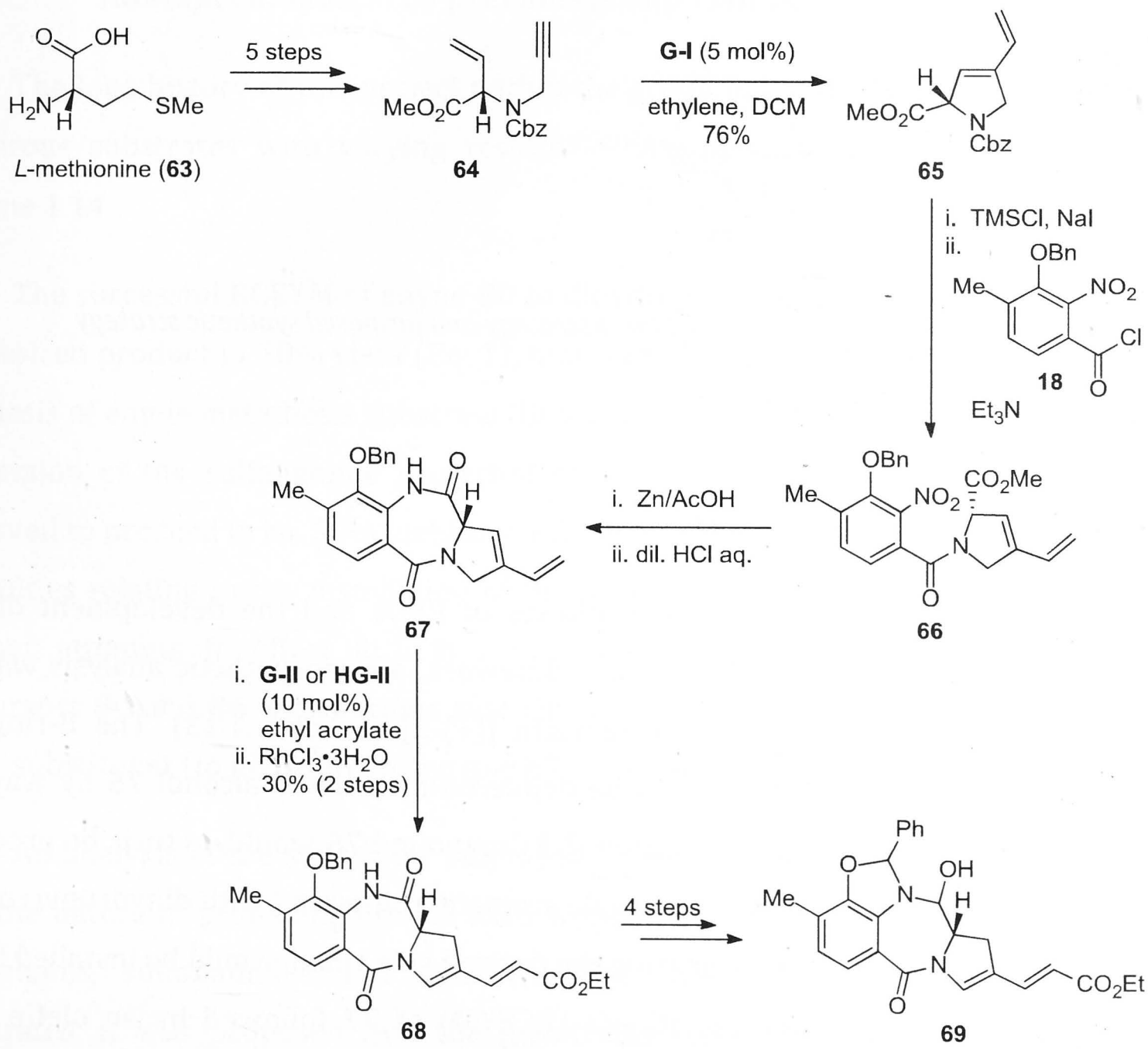


Figure 1.5 *– Catalysts for olefin metathesis*

1.4.2.1 Employing metathesis in the synthesis of PBDs

In 2004, Mori and co-workers used ring-closing enyne metathesis (RCEYM) to install the required diene moiety in their anthramycin analogue **69** (Scheme 1.11).[40] Starting from *L*-methionine (**63**), the metathesis precursor **64** was synthesised in 5 steps. RCEYM was effected with Grubbs' 1st generation catalyst (**G-I**) to form the 2,5-dihydropyrrole **65** – with the double bond in the wrong position. Subsequent deprotection and acylation with benzoyl chloride **18** produced amide **66**, carrying the PBD skeleton with both the A- and C-rings. The B-ring was introduced by reduction of the nitro group to the corresponding aniline followed by condensation with the C-ring ester moiety to give tricycle **67**. Olefin-cross metathesis of the terminal alkene in compound **67** with ethyl acrylate using a more active catalyst [Grubbs' 2nd generation (**G-II**) or Hoveyda Grubbs 2nd generation catalyst (**HG-II**)] introduced the conjugated side chain and subsequent isomerisation using rhodium(III) trichloride gave the desired 2,3-dihydropyrrole **68**. Further deprotection and functional group interconversions gave anthramycin derivative **69**.

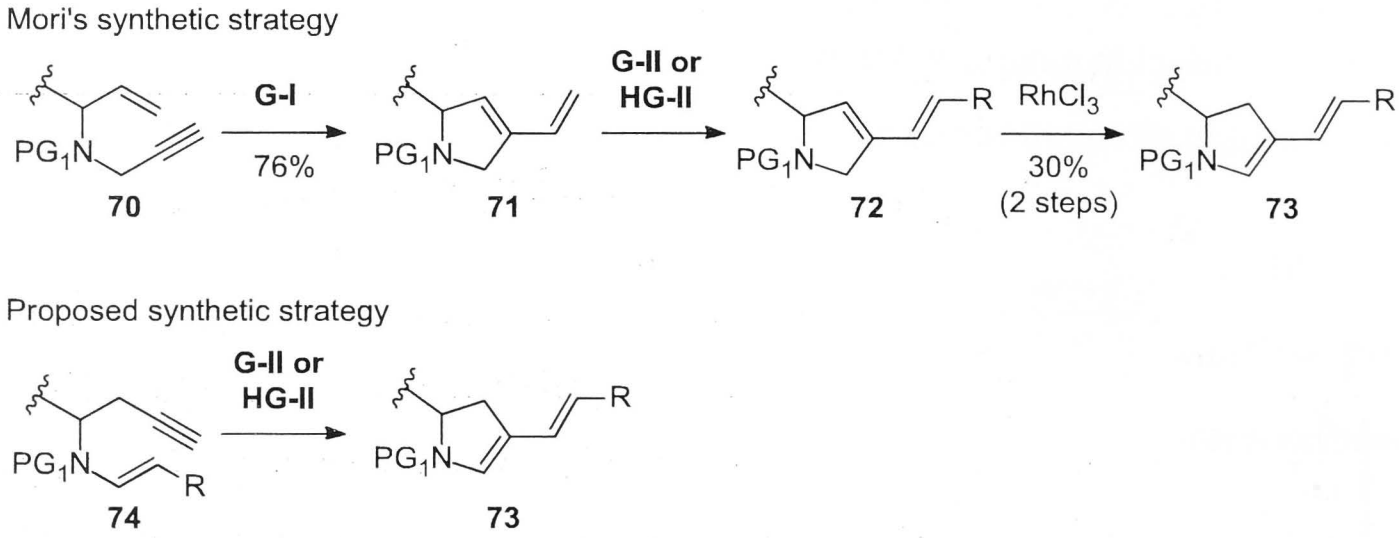


Scheme 1.11 – *Mori synthesis of anthramycin derivative* ***69***[40]

1.5 Proposed strategy for constructing dihydropyrrole moiety

While Mori's synthesis showcased the construction of the dihydropyrrole ring through RCEYM, there were some short comings. The initial RCEYM of enyne **70** to 2,5-dihydropyrrole **71** proceeded smoothly in a good yield. However, the elongation of the side chain using cross metathesis to give compound **72**, which required the additional isomerisation step with rhodium(III) chloride produced the desired 2,3-dihydropyrrole **73** in a low 30% yield over two steps.

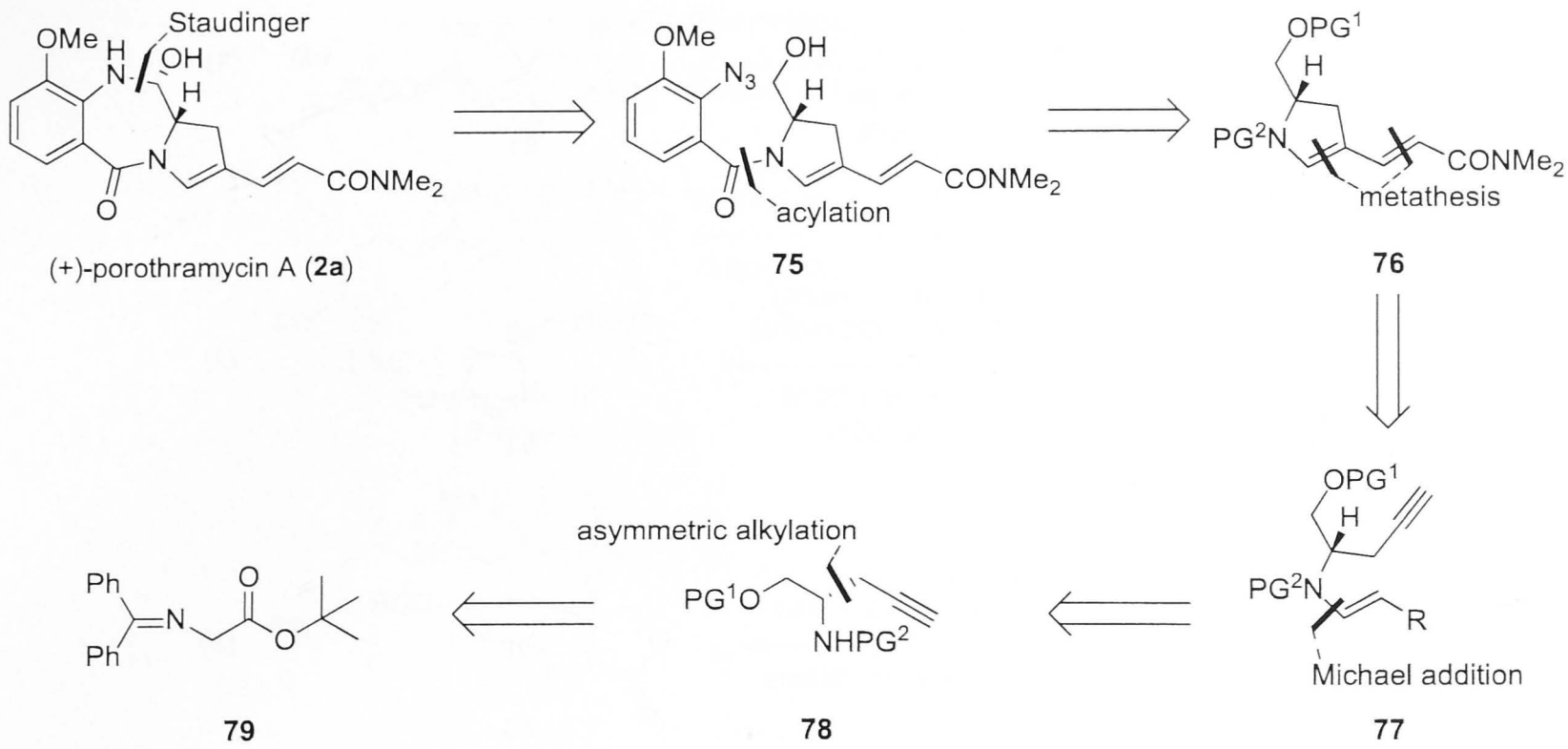
In order to avoid this additional isomerisation step, it was envisaged that effecting a metathesis rearrangement on precursor **74** would deliver the desired 2,3-dihydropyrrole **73** efficiently (Scheme 1.12).



Scheme 1.12 *– Comparison of Mori's strategy and proposed synthetic strategy*

1.5.1 Retrosynthetic analysis

After a review of the previous syntheses of PBDs and the development of new strategies for the construction of the PBD framework, a retrosynthetic analysis was put forward for the synthesis of (+)-porthramycin [(+)-**2**] (Scheme 1.13). The B-ring and resulting N10-C11 carbinolamine could be delivered from azido alcohol **75** by way of a partial oxidation and a Staudinger reaction.[37,38] Compound **75** would, in turn, be produced from a chemoselective acylation of a suitable aromatic compound with dihydropyrrole **76**. The protected dihydropyrrole **76**, bearing the desired side chain, would be installed by the key step, a ring closing enyne metathesis (RCEYM) of **77** followed by an olefin cross metathesis (OCM). The starting material for the key step can be accessed through an aza-Michael addition of the amine of protected amino alcohol **78**. The functionality and stereocentre observed in compound **78** will be introduced by an asymmetric alkylation of protected glycine imine **79**, followed by functional group interconversions.[41]



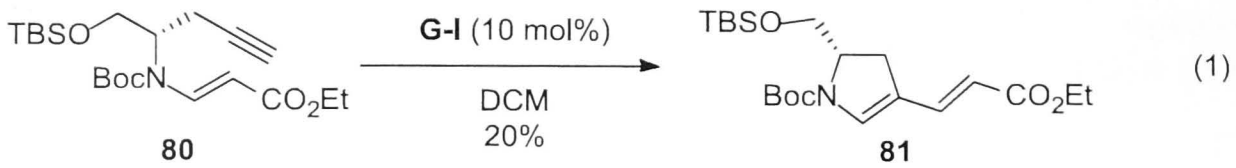
Scheme 1.13 – *Retrosynthetic Analysis*

1.5.2 Attempts at RCEYM by previous group members

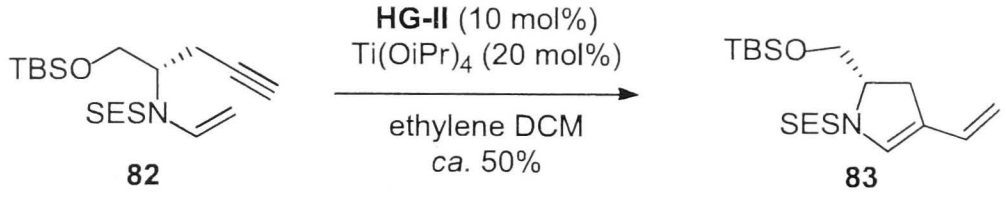
The long history of this project within the group has seen the RCEYM attempted on numerous substrates with varying results.[42,43] A summary of results is presented in Scheme 1.14.

The successful RCEYM of enyne **80** to dihydropyrrole **81** was observed once to give the desired product in 20% yield (Eq. 1), however, this result could not be replicated and synthesis of enyne metathesis substrate **80** was met with difficulties and low yields.[42] The conversion of the sulfonamide protected enyne **82** to dihydropyrrole **83** (Eq. 2) was observed to proceed in *ca.* 50% yield several times however, due to limits on material and difficulties relating to the installation of the *N*-vinyl group, this method was abandoned. Further attempts to effect RCEYM using oxazolidinone protected enyne metathesis precursors **84** and **86** with various side chains (to give dihyropyrrole **85**) or with an *N*-vinyl substituent (to give dihydropyrrole **87**) were unsuccessful.

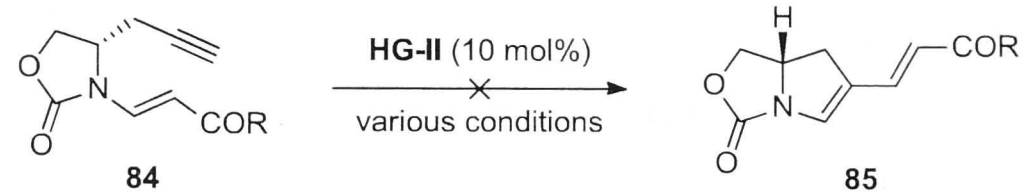
An analysis of the substrates employed in the metathesis rearrangement indicated that the nature of protecting groups used were all electron withdrawing groups such as carbamates, sulfonamides and oxazolidinones. Given the limited success of these substrates, it was proposed that the metathesis rearrangement be attempted with a substrate bearing an electron donating protecting group such as *p*-methoxybenzyl (PMB) in order to investigate the role of the protecting group in aiding the desired transformation.



80 **81** (1)

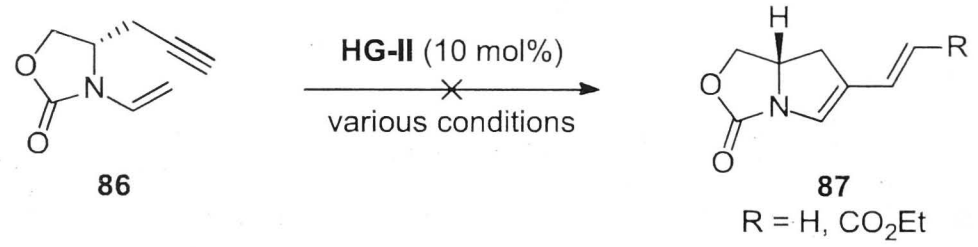


82 **83** (2)



84
R = OEt or NMe_2

85 (3)



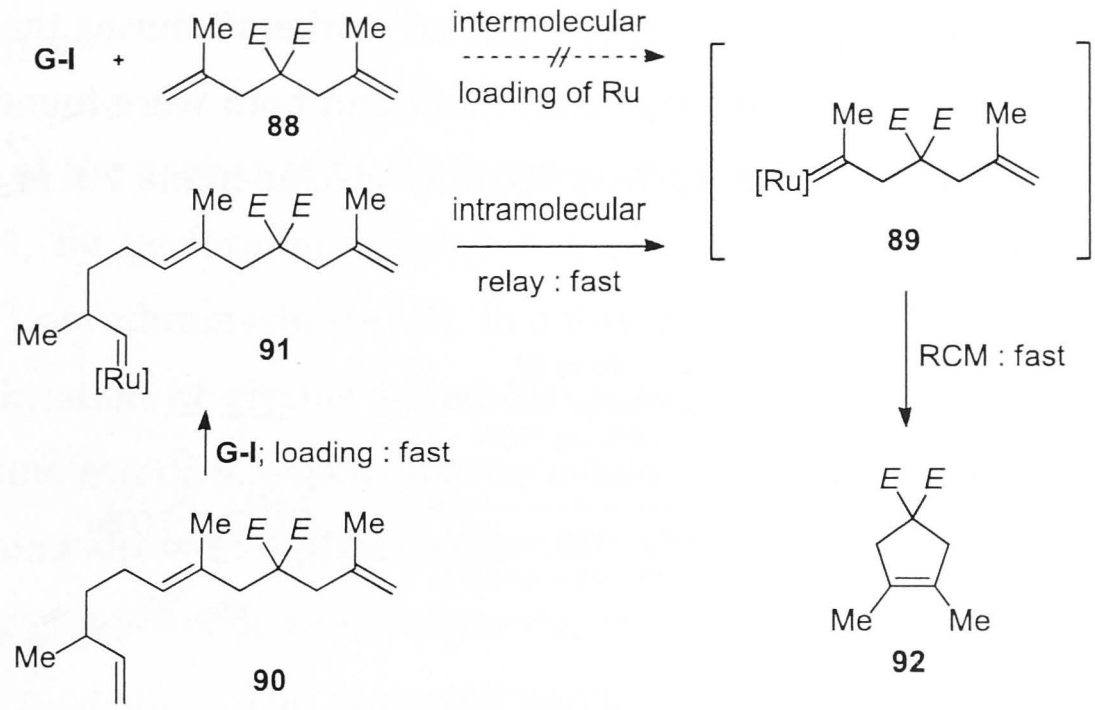
86 **87** (4)
R = H, CO_2Et

Scheme 1.14 *– Previous attempts on RCEYM to form 5-membered C-ring*

It can also be argued that the inability of the substrates to undergo RCEYM may be due to the inactivity of the *N*-vinyl alkene, thus leading to no or very slow initiation with the ruthenium catalyst. As such, it was hoped that relay-ring closing metathesis (RRCM) could be applied to our substrate in order to aid the loading of the ruthenium into the correct position and subsequently provide the desired dihydropyrrole.

1.5.3 Relay-ring closing metathesis

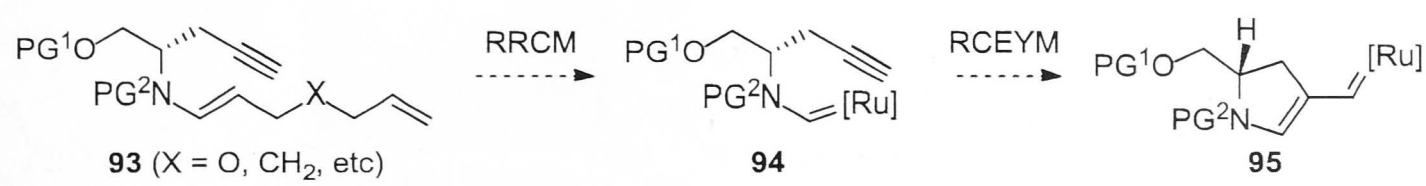
An excellent example of the advantages of using relay metathesis was demonstrated by Hoye and co-workers in 2004 (Scheme 1.15).[44] Using diene **88** bearing two 1,1-disubstituted ethylene units, Hoye demonstrated that it was not possible to do a ring closing metathesis (RCM) as loading of the catalyst did not occur to give ruthenium carbene **89**. However, when starting from triene **90**, now bearing a monosubstituted alkene unit, ruthenium was readily loaded onto the double bond (**91**) and a kinetically favoured RCM then relays the ruthenium onto the previously unreactive 1,1-disubstituted olefin to give the desired ruthenium carbene **89**. A second RCM then takes place to give the cyclic product **92**.



Scheme 1.15 *– Example of relay-ring closing metathesis by Hoye and co-workers[44]*

All reactions done in DCM, 45 °C; E = CO_2Et

It was proposed that by using a substrate bearing a tethered terminal olefin , such as in compound **93**, the ruthenium catalyst could be relayed onto the *N*-vinyl alkene (**94**) and subsequent RCEYM would deliver the desired dihydropyrrole **95** (Scheme 1.16).



Scheme 1.16 *– Proposed relay-ring closing metathesis substrate **93***

1.5.4 Phase transfer catalysis

The above-mentioned synthetic plan (Section 1.5.1) requires the synthesis of the protected amino alcohol building block **78** in a stereoselective manner from glycine imine **79** (Scheme 1.13). Previous studies within the group have indicated that the introduction of the desired (*S*)-stereocentre can be done by an asymmetric alkylation using organocatalysts.[41,45] More specifically, the transformation can be performed using cinchona-derived phase-transfer catalysts (PTCs), such as **96** and **97**.

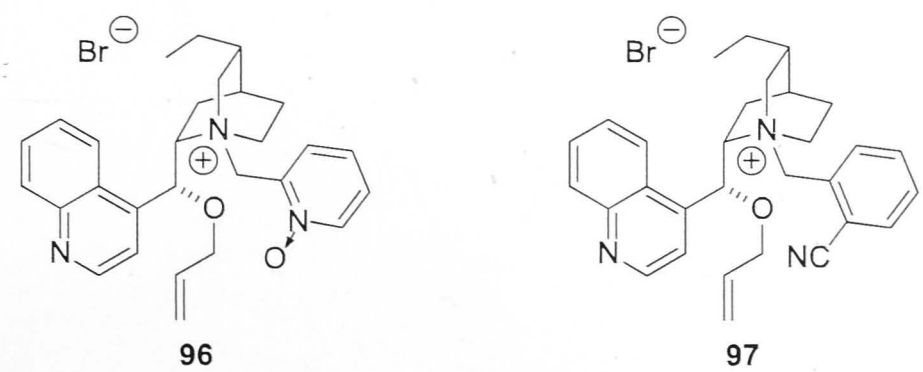
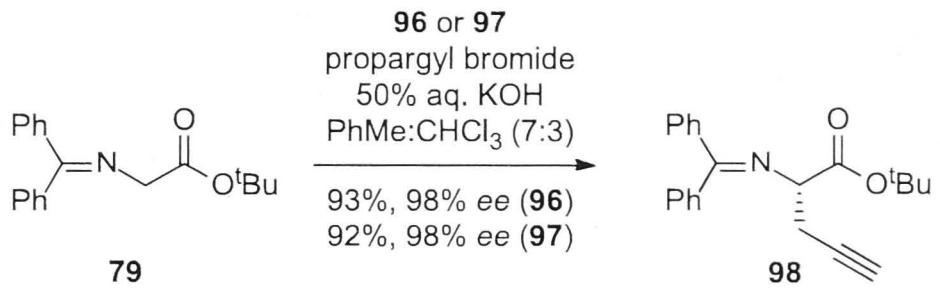


Figure 1.6 *– Cinchona-derived phase transfer catalysts for asymmetric alkylation[46]*

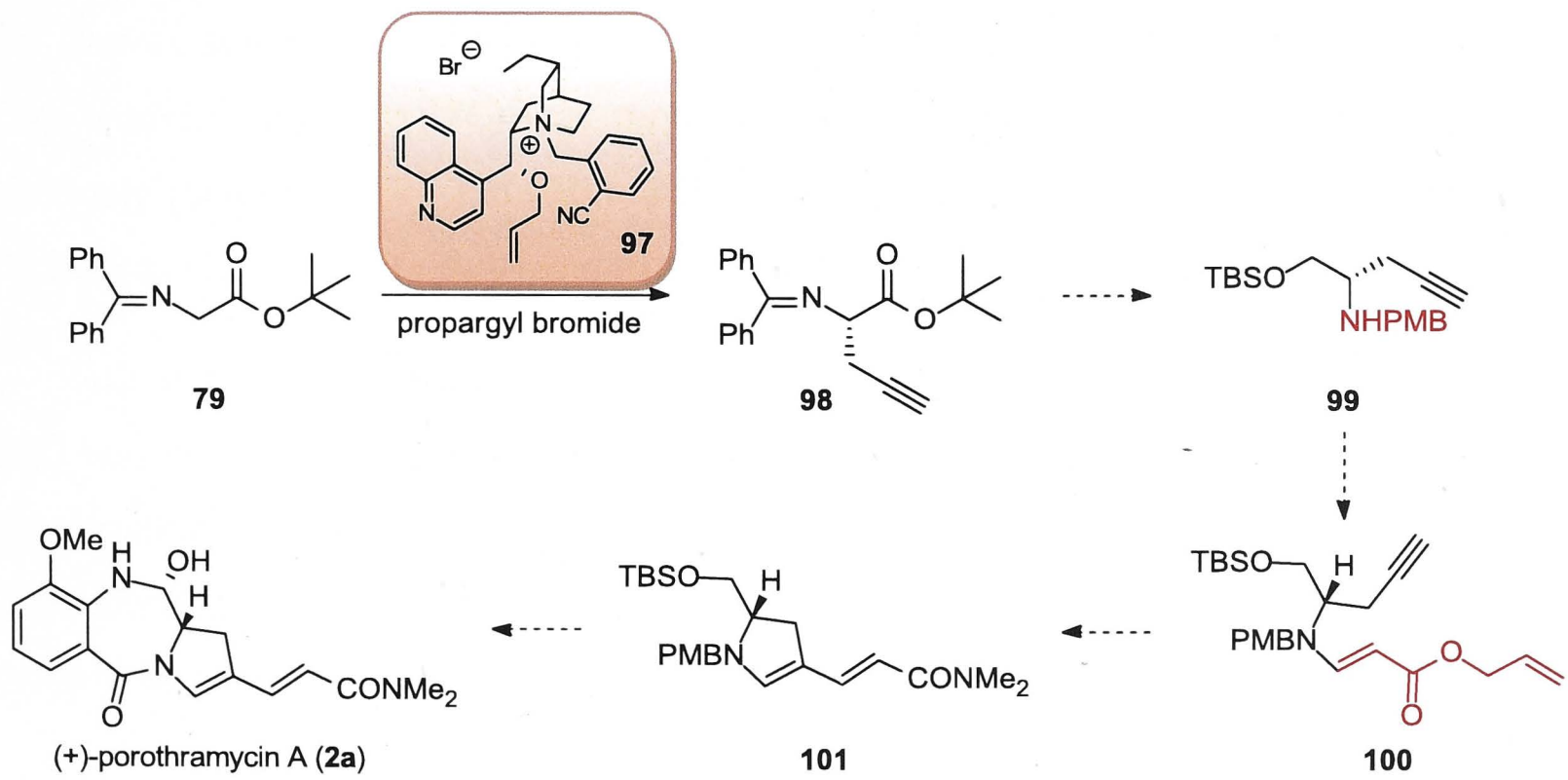
These catalysts were developed by Jew and co-workers[46] during their investigation into the electronic effects of the N^+ arylmethyl unit and both were found to deliver the desired α-substituted amino esters, such as **98**, from glycine imine **79**, in excellent yields and *ee*'s (Scheme 1.17).



Scheme 1.17 – *Example of asymmetric alkylation using phase-transfer catalysts* ***96*** *and* ***97***

1.6 Aims

The aim of the project is to synthesise the dihydropyrrole moiety, as observed in compound **101**, by performing a relay-ring closing metathesis en route to the total synthesis of (+)-porothramycin [(+)-**2**]. In a forward sense, this would firstly involve the asymmetric alkylation of glycine imine **79** in the presence of PTC **97** to give the α-substituted amino ester **98**, which after several functional group interconversions would provide the amino alcohol **99** protected as the PMB amine (Scheme 1.18). The use of the PMB protecting group will be used to investigate the effect of the protecting group on the metathesis rearrangement. The protected amino alcohol **99** would then participate in an aza-Michael addition reaction to give the metathesis substrate **100** containing the tether required for a relay ring closing metathesis. Subsequent RRCM would hopefully deliver the dihydropyrrole which can be further elaborated to dimethylamide **101** and used to access porothramycin A (**2a**)



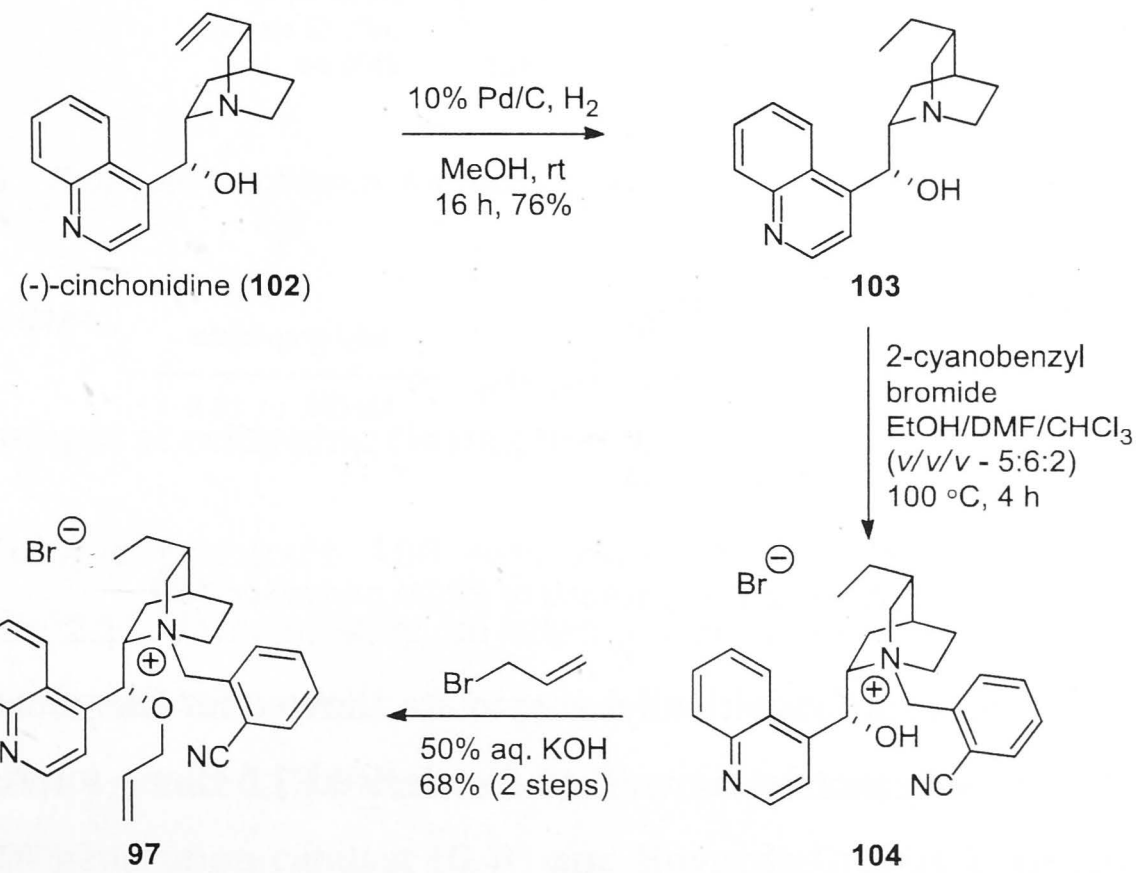
Scheme 1.18 – *Proposed synthetic route to (+)-porothramycin A [(+)-2**a**]*

Chapter 2 Dihydropyrrole synthesis *via* relay-ring closing metathesis

2.1 Synthesis of phase-transfer catalyst 97

Before synthesis of our metathesis substrate could commence, the synthesis of the phase transfer catalyst (PTC) was required for the asymmetric alkylation. As observed previously (Scheme 1.17), PTC **96** and **97** both gave similar yields and *ee*'s and as such PTC **97** was chosen for its shorter synthetic route.

Following a synthetic sequence reported by Jew and co-workers, (–)-cinchonidine (**102**) was subjected to palladium on charcoal under a hydrogen atmosphere to give (–)-hydrocinchonidine (**103**) in good yield (Scheme 2.1).[46] Subsequent *N*-alkylation with 2-cyanobenzyl bromide produced the ammonium bromide salt **104** and *O*-allylation afforded the desired PTC **97** in 52% overall yield from (–)-cinchonidine (**102**).

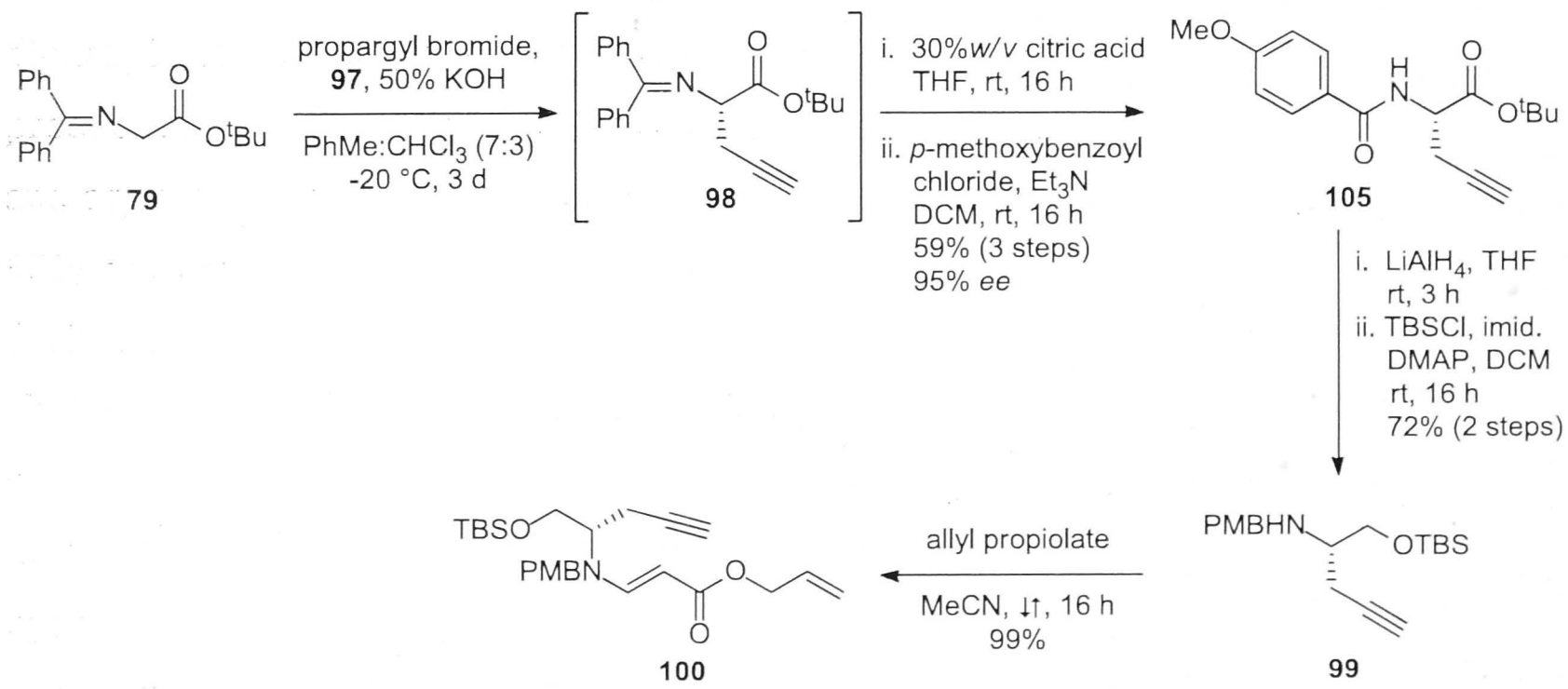


Scheme 2.1 – *Preparation of Phase Transfer Catalyst 97*[46]

2.2 Synthesis of relay ring closing metathesis precursor – PMB

With PTC **97** in hand, synthetic efforts were turned towards the synthesis of relay-ring closing metathesis (RRCM) precursor **100**.

The synthesis began with the alkylation of readily available glycine imine **79** in the presence of PTC **97** and propargyl bromide, as described by Jew and co-workers, to give the α-substituted amino ester **98** (Scheme 2.2).[46] Due to potential sensitivity of the diphenylmethylidene protecting group to flash chromatography on silica, the alkylated product **98** was not isolated but instead deprotected in the presence of aqueous citric acid and acylated with *p*-methoxybenzoyl chloride to give amido ester **105** in 59% yield and 95% *ee* from imine **79**. The formation of the *p*-methoxybenzoyl amide as opposed to the desired *p*-methoxybenzyl (PMB) derivative was due to ease of access to the former and ability to access the latter using reduction conditions in the next step. This synthetic strategy also eliminated the possibility of over alkylation in the presence of PMB-Cl to give dibenzylamines. Amido ester **105** was subsequently reduced with lithium aluminium hydride to give the primary alcohol, which was then protected as the *tert*-butyldimethylsilyl (TBS) ether to give the protected amino alcohol **99**. The aza-Michael addition to readily synthesised allyl propiolate posed some minor challenges however, changes in solvent and temperature ultimately produced the aza-Michael adduct **100** in good yields.

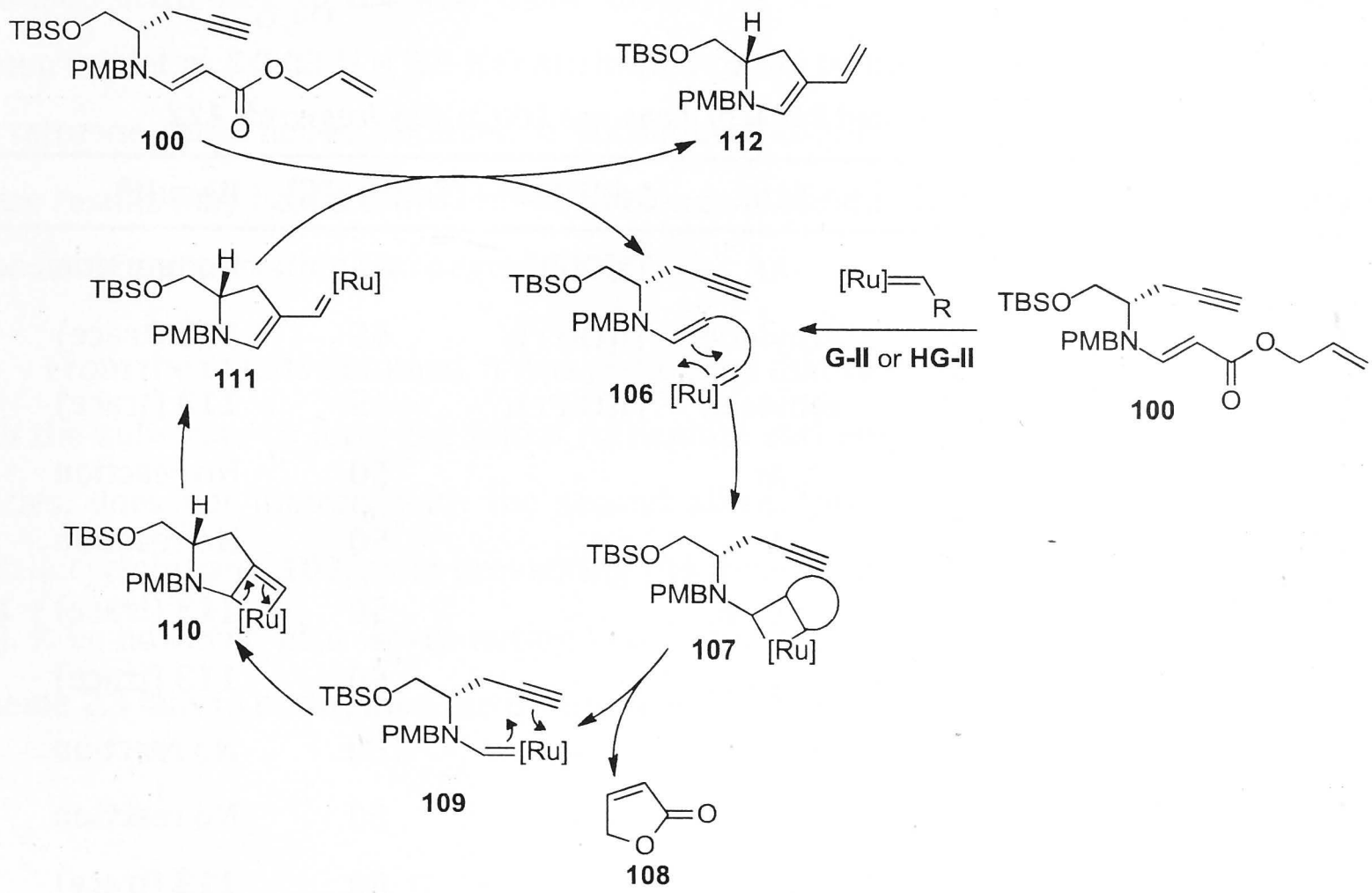


Scheme 2.2 *– Synthesis of RRCM precursor* ***100***

The aza-Michael addition with allyl propiolate allowed for the efficient introduction of the required enamine moiety, as well as the desired 1,6-diene for relay-ring closing metathesis (RRCM).

2.2.1 Proposed mechanism for metathesis rearrangement

Having successfully synthesised the desired metathesis substrate **100**, it was proposed that in the presence of a ruthenium catalyst, the diene-yne **100** would deliver the dihydropyrrole **112** (Scheme 2.3). This would occur by the initial loading of the ruthenium catalyst onto the terminal alkene to give ruthenium carbene **106**, which would subsequently undergo a cyclisation to metallocyclobutane **107** and ring opening to produce a cyclic alkene byproduct, butenolide **108**, and a second ruthenium carbene **109**. This species would then undergo another cyclisation to give the metallocyclobutene **110**, which would ring open to give vinyl carbene **111**. Re-entry of the substrate, diene-yne **100**, would then deliver the dihydropyrrole **112** and the ruthenium carbene **106** which can then carry on in the cycle.

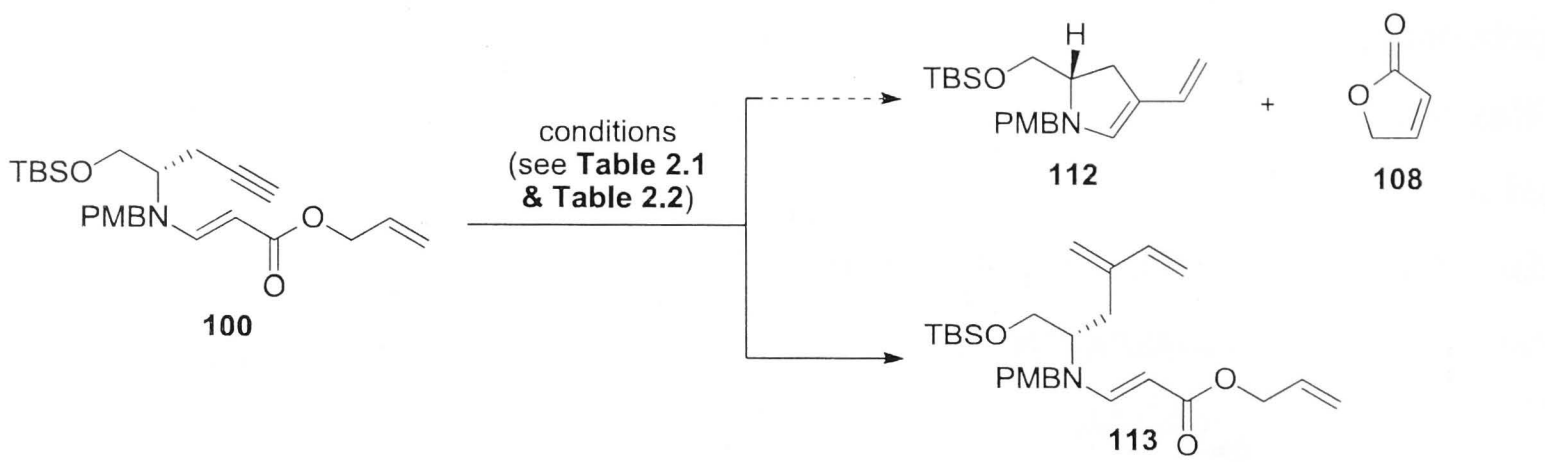


Scheme 2.3 *– Proposed mechanism for metathesis of diene-yne* ***100*** *to dihydropyrrole* ***112***

2.2.2 Attempts at relay ring closing metathesis

The metathesis precursor **100** was subjected to various metathesis reaction conditions (Table 2.1). Unfortunately, all attempts to obtain the desired dihydropyrrole **112** were unsuccessful and resulted in either no reaction or the formation of the undesired tetraene product **113** (Scheme 2.4). The catalysts employed for these reactions were Grubbs' 2nd generation catalyst (**G-II**) and Hoveyda-Grubbs 2nd generation catalyst (**HG-II**) as they were readily available and known to be more reactive than Grubbs' 1st

generation catalyst (**G-I**).[47] The solvents and temperatures chosen for the reactions were all typical of those employed for metathesis rearrangements. The use of titanium isopropoxide as an additive was also trialed to disrupt potential coordination of the ruthenium complex to the heteroatoms present.[48] All reactions were performed on a small scale and as such, the results of the reactions were determined after analysis by ESI mass spectroscopy.



Scheme 2.4** – Attempted RRCM of diene-yne **100** to dihydropyrrole **112

Entry	Catalyst†	Solvent	Atm.	Additive‡	Temp (°C)	Result*
1	**HG-II**	DCM	Ar	$Ti(OiPr)_4$	45	No reaction
2	**HG-II**	DCM	ethylene	$Ti(OiPr)_4$	45	**113** (trace)
3	**G-II**	DCM	ethylene	$Ti(OiPr)_4$	45	**113** (trace)
4	**HG-II**	C_6D_6	Ar	-	50	No reaction
5	**G-II**	C_6D_6	Ar	-	50	No reaction
6	**HG-II**	C_6D_6	Ethylene	-	50	**113** (trace) + **100**
7	**G-II**	C_6D_6	Ethylene	-	50	**113** (trace)
8	**G-II**	toluene	Ar	-	80	No reaction
9	**HG-II**	toluene	Ar	-	80	No reaction
10	**G-II**	toluene	Ethylene	-	80	**113** (trace)
11	**HG-II**	toluene	Ethylene	-	80	**113** (trace)

***Table 2.1** – Conditions used for RRCM/RCEYM of **100**; †10 mol% catalyst loading for all reactions unless otherwise stated; ‡20 mol% of additive was used in all reactions unless otherwise stated*

**Results determined by analysis of ESI^+ MS*

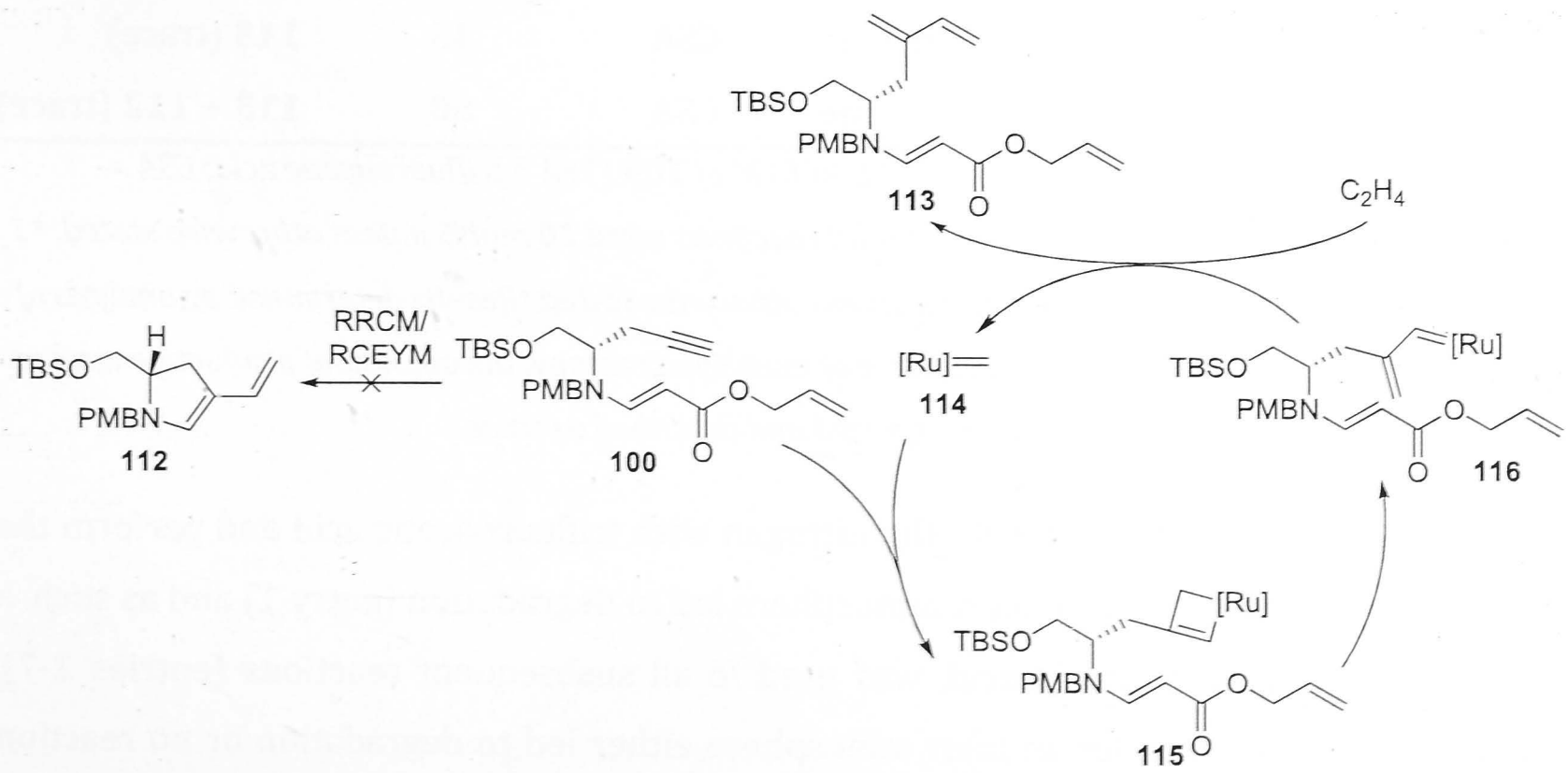
Attempts to perform the metathesis rearrangement under an inert (argon) atmosphere at various temperatures with (entry 1) or without (entries 4, 5, 8, 9) titanium isopropoxide present, led to no reaction.

To overcome the difficulties faced under an argon atmosphere, the reactions were attempted under an atmosphere of ethylene (entries 2, 3, 6, 7, 10, 11) which may accelerate and encourage the turnover of vinyl carbene **111** to deliver dihydropyrrole **112** in the metathesis reactions.[49] Unfortunately, in all instances where ethylene was

employed, the formation of the undesired tetraene **113** – derived from the enyne cross metathesis between ethylene and the alkyne moiety within the molecule (Scheme 2.4) – was observed. This was determined by the analysis of the ESI mass spectrum obtained from the crude reaction mixture which displayed ions corresponding to the proton adduct and sodium adduct of tetraene **113**, at *m/z* 372 and 394 respectively.

Due to the small scale nature of these reactions, typically 5-10 mg, and the non-quantitative nature of mass spectroscopy, the amount of product generated has been reported and described as trace. A crude ^{1}H NMR spectrum obtained of the undesired tetraene **113** confirmed the formation of the ethylene cross-metathesis product. It showed a spectrum very similar to that of the starting dienyne **100** with the addition of a one proton doublet of doublets at δ 6.30 (J = 17.7, 10.8 Hz) and a four proton multiplet at δ 5.10-5.00 attributed to the new diene moiety as well as the disappearance of the one proton triplet at δ 2.03 (J = 2.8 Hz) attributed to the terminal alkyne. A cleaner sample of the tetraene could not be obtained as subsequent columns led to significant loss of mass. These results may be attributed to the presence of residual amounts of ruthenium leading to possible complexation and degradation.

From the results obtained, it was postulated that the catalyst either does not interact with the substrate to form the initial ruthenium carbene **106** or, after formation of this species, does not interact with the second alkene present in the molecule to produce metallocyclobutane **107**, thus preventing the formation of dihydropyrrole **112** (Scheme 2.3). It is, however, also worth noting that if any step of the catalytic cycle presented in Scheme 2.3 fails to occur, then the production of dihydropyrrole **112** would not proceed.



Scheme 2.5 – *Enyne cross metathesis of ethylene with diene-yne* ***100***

The formation of the tetraene byproduct **113** involves the alkyne moiety of the substrate **100** participating in an enyne cross metathesis with ruthenium carbene **114**, derived from the reaction of either G-II or HG-II with ethylene, to produce metallocyclobutene **115**. Subsequent ring opening delivers vinyl carbene **116** which, itself, undergoes a cross metathesis with ethylene to generate the tetraene **113**, with the allyl ester moiety intact. The ruthenium carbene species **114** can then interact with another molecule of metathesis precursor **100** and maintain the cycle.

It was postulated that the failure in affecting the RRCM and the formation of tetraene **113** under ethylene conditions, was due to the poor reactivity of the electron rich enamine in substrate **100**. Thus, to overcome this problem, it was proposed that the nitrogen be protonated to produce a comparatively electron-deficient species.

Protonation of the amine was attempted using both trifluoroacetic acid (TFA) and camphorsulfonic acid (CSA) (Scheme 2.4 & **Table 2.2**).[50] Once again, a variety of metathesis reactions conditions were trialled and unfortunately the desired dihydropyrrole **112** could not be obtained.

Entry	Catalyst†	Solvent	Atm.	Additive‡	Temp. (°C)	Result*
1	**G-II**	DCM	Ar	TFA	45	Degradation
2	**G-II**	DCM	Ar	CSA	45	no reaction
3	**HG-II**	DCM	Ar	CSA	45	no reaction
4	**HG-II**	toluene	Ar	CSA	80	Degradation
5	**G-II**	DCM	Ethylene	CSA	45	**113** (trace)
6	**HG-II**	DCM	Ethylene	CSA	45	**113** (trace)
7	**HG-II**	toluene	Ethylene	CSA	80	**113** + **112** (trace)

Table 2.2 *– Conditions used for RRCM/RCEYM of* ***100*** *(TFA = trifluoroacetic acid; CSA = camphorsulfonic acid; †Catalyst loading for all reactions were 10 mol% unless otherwise stated; ‡1 eq. of additive was used in all reactions unless otherwise stated *Results determined by analysis of ESI⁺ MS - due to the non-quantitative nature of mass spectroscopy, the amount of product generated has been reported and described as trace.*

Initial attempts to protonate the nitrogen with trifluoroacetic acid and perform the metathesis reaction under an inert atmosphere led to degradation (entry 1) and as such, a milder acid, camphorsulfonic acid, was used in all susbsequent reactions (entries 2-7). Attempted reactions under an inert atmosphere either led to degradation or no reaction (entries 2-4) and as a result the use of an ethylene atmosphere was trialled again.

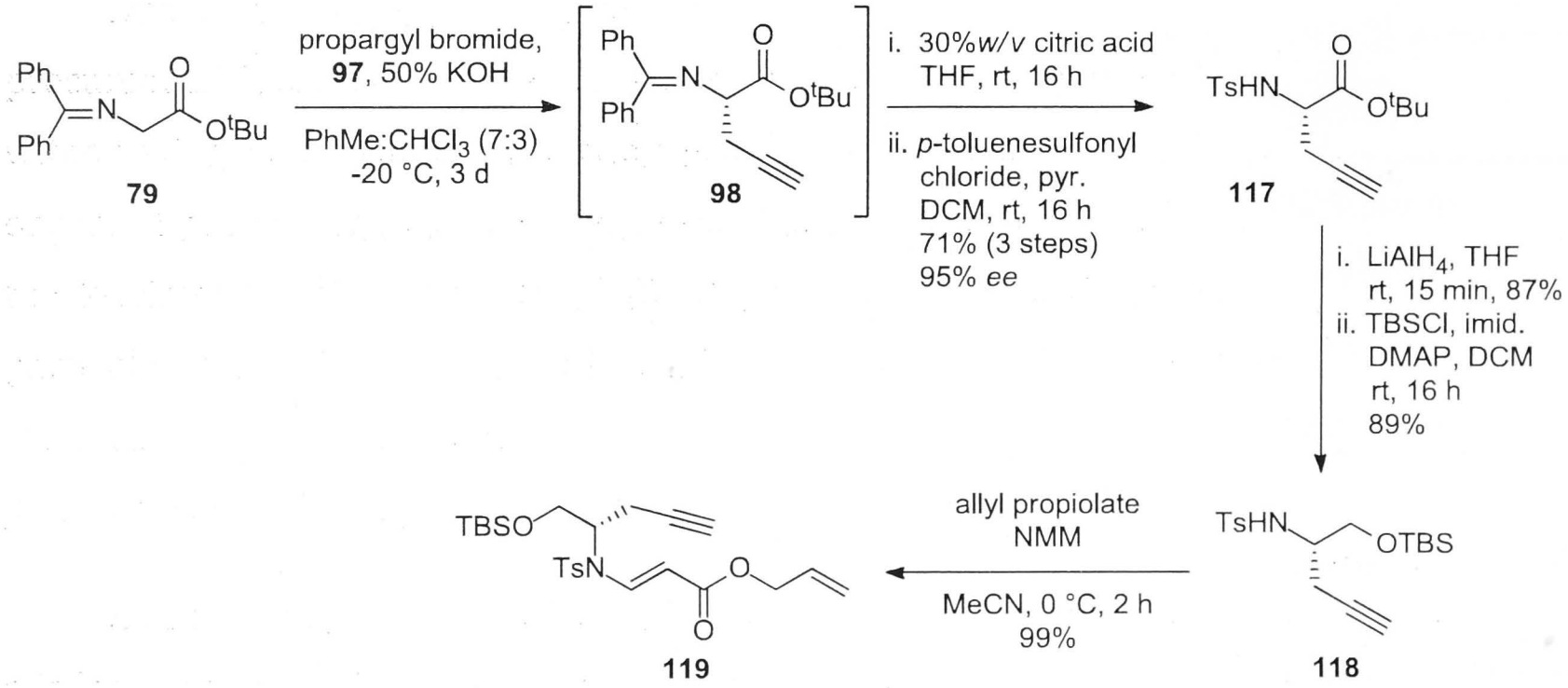
In most cases, the presence of ethylene in the reaction once again led to the formation of tetraene **113** and the appearance of the previously observed resonances at δ 6.30 and δ 5.10-5.00 in the ^{1}H NMR. However, when using toluene as the solvent, in addition to the formation of tetraene **113**, trace amounts of the proton adduct and sodium adduct associated with diene **112** were also observed but no other data could be obtained to conclusively confirm the presence of this structure.

Although this result indicated that an electron deficient enamine was more desirable for the metathesis rearrangement, it also showed that the formation of the tetraene **113** was unavoidable in the presence ethylene.

2.3 Synthesis of relay ring closing metathesis precursor – Ts

Due to the disappointing results obtained from the PMB protected metathesis precursor **100**, it was clear the protecting group needed to be altered. As such, an electron withdrawing sulfonamide protecting group was chosen based on the partial success observed previously (Scheme 1.14). Although the earlier metathesis attempts employed the 2-trimethylsilylethanesulfonyl (SES) protecting group, the need to synthesise this particular protecting group and lack of commercial availability led to efforts being put towards the synthesis of a metathesis precursor bearing the commercially available *p*-toluenesulfonyl (Ts) protecting group.

As such, the *p*-toluenesulfonyl (Ts) protected amine was formed by reprotecting the alkylated product **98** with *p*-toluenesulfonyl chloride to give ester **117** (Scheme 2.6). This product was reduced to the corresponding primary alcohol and was then protected as the TBS ether **118**. The aza-Michael addition of the protected amino alcohol **118** with allyl propiolate proceeded smoothly to produce **119** in good yields.

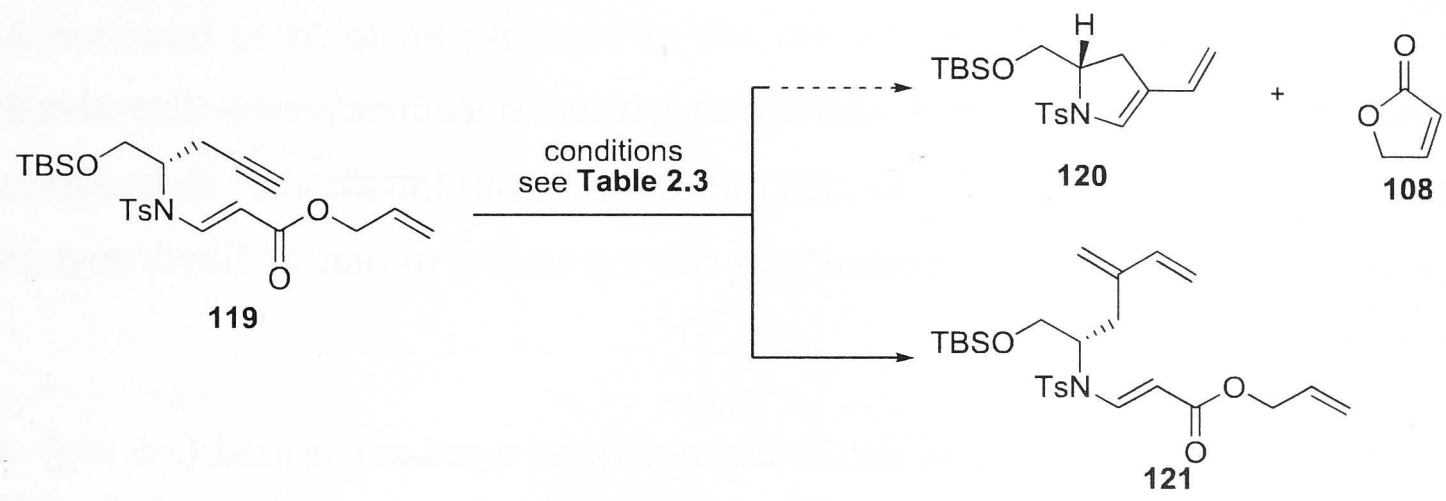


Scheme 2.6 *– Synthesis of RRCM precursor* ***119***

2.3.1 Attempts at relay ring closing metathesis

With a new RRCM/RCEYM precursor **119** in hand, it was subjected to various conditions (Scheme 2.7 & Table 2.3). Analysis of the ESI mass spectrum obtained from the crude mixture of the initial metathesis reaction attempt displayed the proton adduct and sodium adduct associated with dihydropyrrole **120** (entry 1, Table 2.3). The mass spectrum also indicated the presence of starting material indicating an incomplete conversion and as such, an ethylene atmosphere was employed in an attempt to push this reaction to completion.

Unfortunately, as observed previously with precursor **100**, the use of an ethylene atmosphere led to the observation of a proton adduct corresponding to the undesirable enyne cross metathesis product **121** in the ESI mass spectrum – albeit with traces of a proton adduct corresponding to the desired diene **120** (entry 2, Table 2.3). The undesired tetraene **121** was further confirmed by analysis of a crude ^{1}H NMR spectrum which displayed a one proton doublet of doublets at δ 6.20 (J = 17.7, 10.8 Hz), two doublets at δ 5.21 (J = 17.7 Hz) and δ 5.08 (J = 10.8 Hz) and a singlet at δ 4.93 (J = 3.5 Hz) attributed to the new diene moiety. The spectrum also lacked the one proton triplet at δ 1.85 (J = 2.7 Hz) associated with the terminal alkyne.



Scheme 2.7 *– RRCM/RCEYM of diene-yne* ***119***

Entry	Catalyst†	Solvent	Atm.	Additive‡	Temp. (°C)	Result
1	**HG-II**	DCM	Ar		45	**120** (trace) + **119**
2	**HG-II**	DCM	ethylene		45	**121** + **120** (trace)
3	**G-II**	DCM	Ar		45	**120** (trace) + **119**
4	**HG-II**	toluene	Ar		80	**120** (trace) + **119**
5	**G-II**	toluene	Ar		80	**120** (trace) + **119**
6	**HG-II**	DCE	Ar		90	**120** (trace) + **119**
7	**G-II**	DCE	Ar		90	**120** (trace) + **119**
8	**HG-II**	DCM	Ar	Ti(O*i*Pr)$_4$	45	**120** (trace) + **119**
9	**G-II**	DCM	Ar	Ti(O*i*Pr)$_4$	45	**120** (trace) + **119**
10	**HG-II**	toluene	Ar	Ti(O*i*Pr)$_4$	80	**120** (trace) + **119**
11	**G-II**	toluene	Ar	Ti(O*i*Pr)$_4$	80	**120** (trace) + **119**
12	**HG-II**	DCE	Ar	Ti(O*i*Pr)$_4$	90	**120** (trace) + **119**
13	**G-II**	DCE	Ar	Ti(O*i*Pr)$_4$	90	**120** (trace) + **119**

Table 2.3 *– Conditions used for RRCM/RCEYM of* ***119****; †10 mol% catalyst loading for all reactions unless otherwise stated; ‡20 mol% of additive was used in all reactions unless otherwise stated*

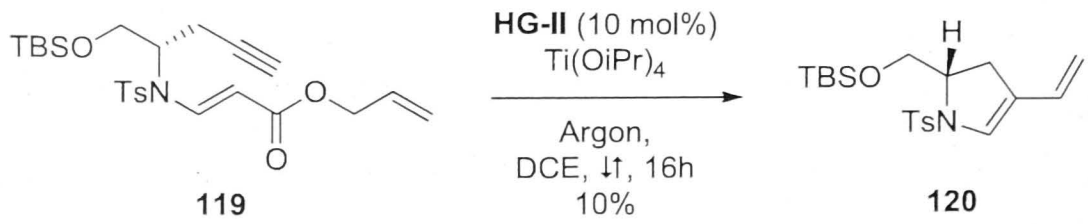
**Results determined by analysis of ESI$^+$ MS - due to the non-quantitative nature of mass spectroscopy, the amount of product generated has been reported and described as trace.*

Since the formation of the tetrane byproduct **121** appeared unavoidable in the presence of ethylene, all subsequent metathesis reactions were performed under an inert atmosphere with variations in the catalyst, solvent and temperature. The reaction conditions explored represent those generally used for metathesis rearrangements. The choice of solvents and thus the resulting temperatures at which the reactions were performed at are limited by the availability of the solvent. The time at which the reactions were stopped were determined by either complete consumption of the starting material or the lack of change observed on the TLC. Attempts to allow the reactions to occur over a longer period of time did not improve the result observed and thus reaction times were generally kept to less than 3 h.

The effect of the Lewis acid additive titanium isopropoxide was also investigated however, it was observed to have no effect on the reaction (entries 8-13). In all reactions attempted, the mass spectrum revealed ions corresponding to that of dihydropyrrole **120** and the starting material **119**.

Due to the small scale upon which the reactions were performed (~5 mg) and the analysis of reaction results using ESI mass spectroscopy, the metathesis was repeated on a larger scale (~20 mg) and was observed to proceed in approximately 10% isolated yield with a 10% catalyst loading (Scheme 2.8). The low yield of the reaction suggested that the rate of catalyst turnover was low or that there were other unknown factors interfering with the catalytic cycle (Scheme 2.9).

The assignment of the structure presented for dihydropyrrole **120** could not be conclusively confirmed as the sample obtained was impure and further attempted purifications of the compound led to decomposition and significant decrease in mass, however, the crude ^{1}H NMR obtained from the reaction had a distinct lack of resonances corresponding to the conjugated allyl ester side chain and also lacked the one proton triplet at δ 1.85 (J = 2.8 Hz) attributed to the terminal alkyne. The mass spectrum displayed ions associated with the proton adduct and sodium adduct at 394 and 416 respectively and the HRMS showed that the species were of the expected composition.



Scheme 2.8

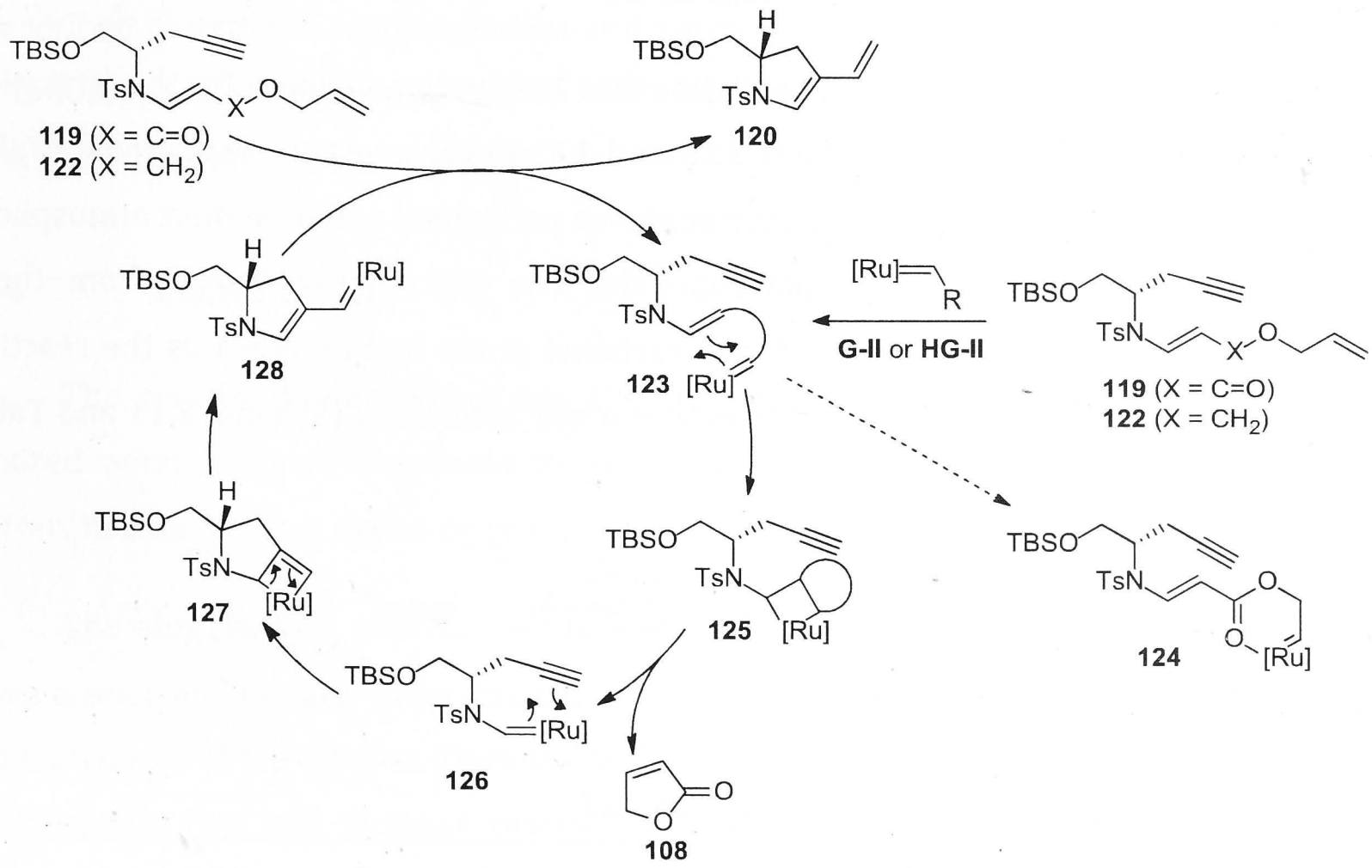
More recent efforts to perform the metathesis rearrangement with a 50% catalyst loading in the hope of obtaining sufficient amounts of material to characterise were

unsuccessful and it was postulated that subjection of the compound to flash chromatography and residual ruthenium present, even after chromatography, led to the degradation of the desired compound. As such, further attempts to isolate the compound were not pursued.

2.3.2 Possible interferences in the metathesis reaction

2.3.2.1 New substrate for RRCM/RCEYM

A potential point of interference in the catalytic cycle involved the co-ordination between the ruthenium and the carbonyl oxygen to form a species such as **124** and in doing so tying up the ruthenium and hindering its ability to perform metathesis reactions (Scheme 2.9).

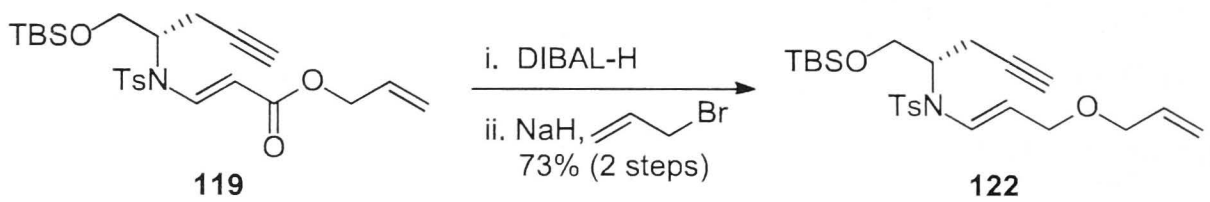


Scheme 2.9

The chelation of heteroatoms, especially the carbonyl oxygen, to the active ruthenium complex is a known occurrence which can significantly alter the activity of the catalyst through the formation of a stable complex.[51,52] In 1996, Fürstner and Langmann postulated that the result of a low yielding metathesis reaction on a homoallylic ester was due to sequestering of the catalyst in the form of an unproductive chelate complex of the ester carbonyl in proximity to the ruthenium carbene intermediate.[53] This phenomenon was also encountered in their synthesis of gloeosporone published in 1997, wherein they

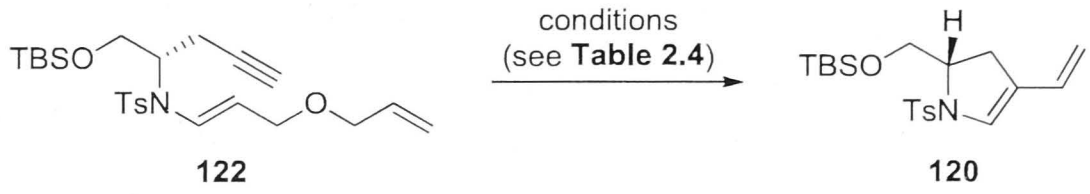
described a resolution for the problem in the form of using a binary catalyst system involving the ruthenium catalyst and titanium isopropoxide.[48]

Unfortunately, the application of the binary catalyst system on substrate **119** did not lead to an increase in the formation of the desired product **120** and thus a solution was sought to permanently remove carbonyl functionality by designing a new substrate bearing an ether functionality to investigate the impact of potential co-ordination of the carbonyl oxygen to ruthenium. The allyl ether precursor **122** was accessed by a reduction of **119** with DIBAL-H and subsequent *O*-allylation with sodium hydride and allyl bromide to form the desired compound in an unoptimised 73% yield (Scheme 2.10).



Scheme 2.10

Due to the limited amount of the allylic ether **122** and precedence for the formation of the enyne cross metathesis products **113** and **121** in the presence of ethylene (Table 2.1 & Table 2.3), the metathesis rearrangement was performed under an inert atmosphere both with and without titanium isopropoxide. The outcomes obtained from these reactions indicated that the removal of the carbonyl group had no effect as the reaction was still stalling well before the starting material was consumed (Scheme 2.11 and Table 2.4).



Scheme 2.11

Entry	Catalyst†	Solvent	Atm.	Additive‡	Temp. (°C)	Result
1	**HG-II**	DCE	Ar		90	**120** (trace) + **122**
2	**HG-II**	DCE	Ar	$Ti(OiPr)_4$	90	**120** (trace) + **122**

***Table 2.4** – Conditions used for RRCM/RCEYM Metathesis of **122**; †10 mol% catalyst loading for all reactions unless otherwise stated; ‡20 mol% of additive was used in all reactions unless otherwise stated *Results determined by analysis of ESI^+ MS - due to the non-quantitative nature of mass spectroscopy, the amount of product generated has been reported and described as trace.*

The comparable results obtained from the attempted relay-ring closing metathesis of both the allyl ester **119** and allyl ether **122** precursor suggest that co-ordination of the

carbonyl oxygen to ruthenium, if present, is not the only feature retarding turnover of the catalyst and perpetuation of the catalytic cycle.

2.3.2.2 Catalyst turnover

A factor associated with a successful catalytic cycle in enyne metathesis reactions involves the interaction of another molecule of substrate, **119** or **122**, with vinyl carbene **128** to release the dihydropyrrole **120** and regenerate the ruthenium carbene **123** which can go on to perpetuate the cycle (Scheme 2.9).

It was hoped that the employment of ethylene in the cycle could aid turnover of the catalyst, however, the results obtained have demonstrated that the use of ethylene did not aid the reaction but instead acted as a partner for the competing cross metathesis reaction to produce tetraene **121**.

These results have led to the belief that the substrate designed is not suitable for the prescribed metathesis rearrangement and a new substrate would need to be designed so as to incorporate functionality which will allow for better reactivity and turnover of the catalyst without the need for ethylene.

2.4 Conclusion

The results obtained from this chapter demonstrate that for the purpose of the desired metathesis rearrangement, the use of an electron withdrawing protecting group is better than an electron donating group.

The observations also indicate that the substrates (**119** and **122**) bearing a tether have a poor ability to re-enter the catalytic cycle, subsequently leading to low yield and slow turnover of the catalyst. Thus, the substrate will need to be redesigned to incorporate functionality that will increase reactivity of the substrate and aid turnover leading to perpetuation of the catalytic cycle.

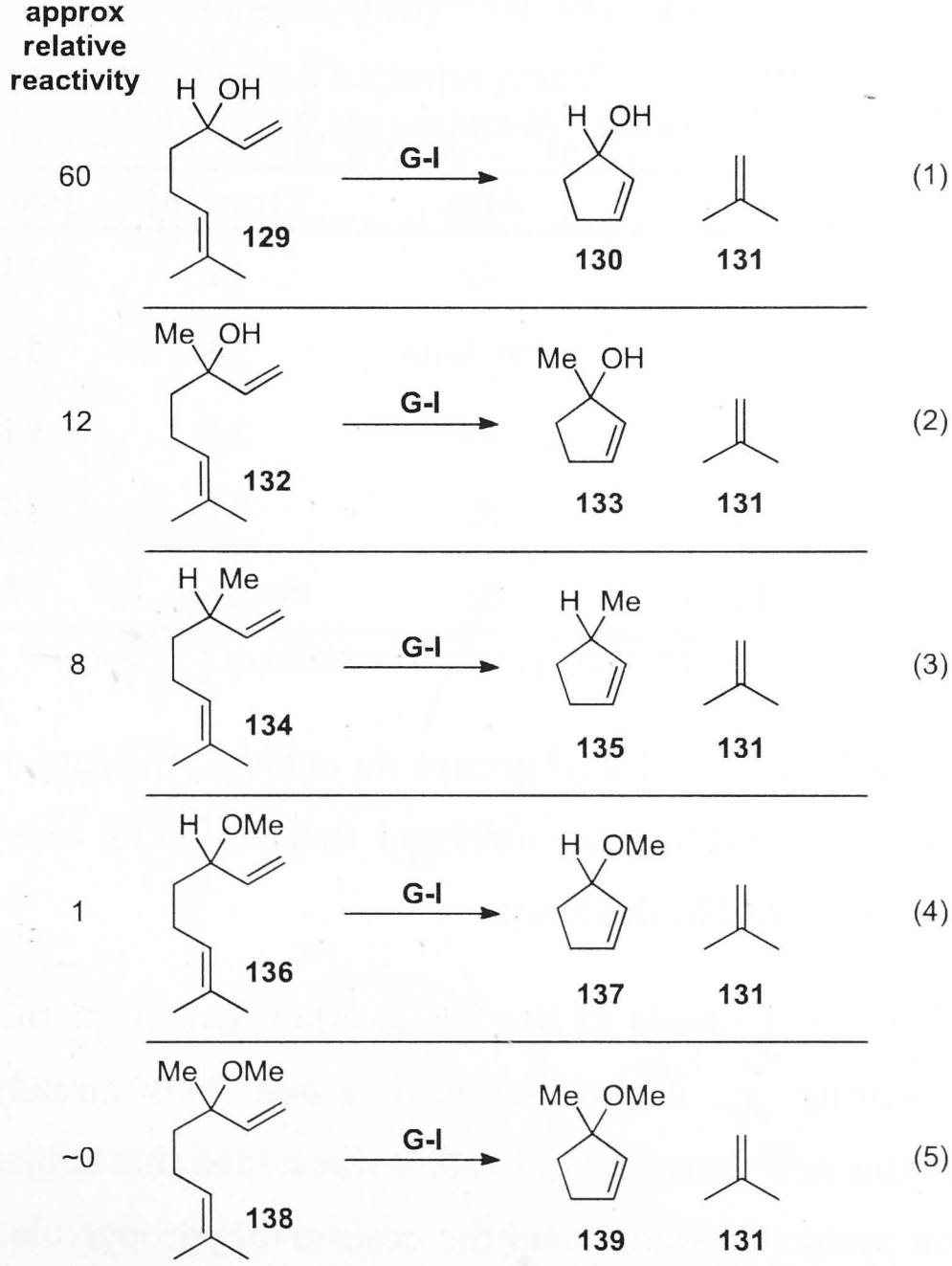
Chapter 3 Dihydropyrrole synthesis

3.1 A new metathesis substrate

As the devised plan utilising relay-ring closing metathesis had not produced the desired result, a new substrate possessing functionality which would promote its re-entry into the catalytic cycle and aid turnover of the catalyst was sought.

3.1.1 Metathesis promoted by allylic alcohols

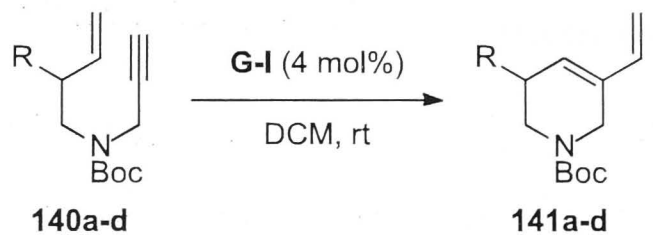
Literature reveals that the presence of an allylic alcohol can greatly enhance the rate of metathesis reactions. This has been highlighted in an example by Hoye and co-workers which compared the relative rate of reaction of allylic alcohols and allylic ethers (Scheme 3.1).[54] In their study, they demonstrated that the presence of an allylic hydroxyl group greatly increased the rate of reaction when compared to compounds with similar steric bulk (eq. 1 & 3; eq. 2 & 4).



Scheme 3.1 *– Relative reactivity of metathesis substrates bearing allylic alcohols and ethers*

Another study performed by Imahori and co-workers on the allylic hydroxyl effect in RCEYM also demonstrated that the increase in activity was also observed in this particular type of metathesis (Scheme 3.2 and Table 3.1).[55]

In the absence of an allylic substituent, RCEYM of substrate **140a** under and inert atmosphere resulted in a low yield of product **141a** (entry 1). However, when an ethylene atmosphere was employed to aid turnover of the catalyst and re-entry of the substrate, the reaction time greatly decreased and the yield increased to 96% (entry 2). This result indicated that the substrate alone is not very active to RCEYM and an additional element allowing for the increase in reactivity was required. On the other hand, substrate **140b**, which contains an allylic hydroxyl group, undergoes RCEYM efficiently under an inert atmosphere to provide the product **141b** in near quantitative yield in 1.5 h (entry 3) indicating that it is a far more active substrate. When the hydroxyl group is protected, as observed in entries 4 and 5, the rate of reaction is similar to that of the unsubstituted substrate **140a** further indicating that hydroxyl groups enhance the rate of reaction while ethers do not.



140a-d **141a-d**

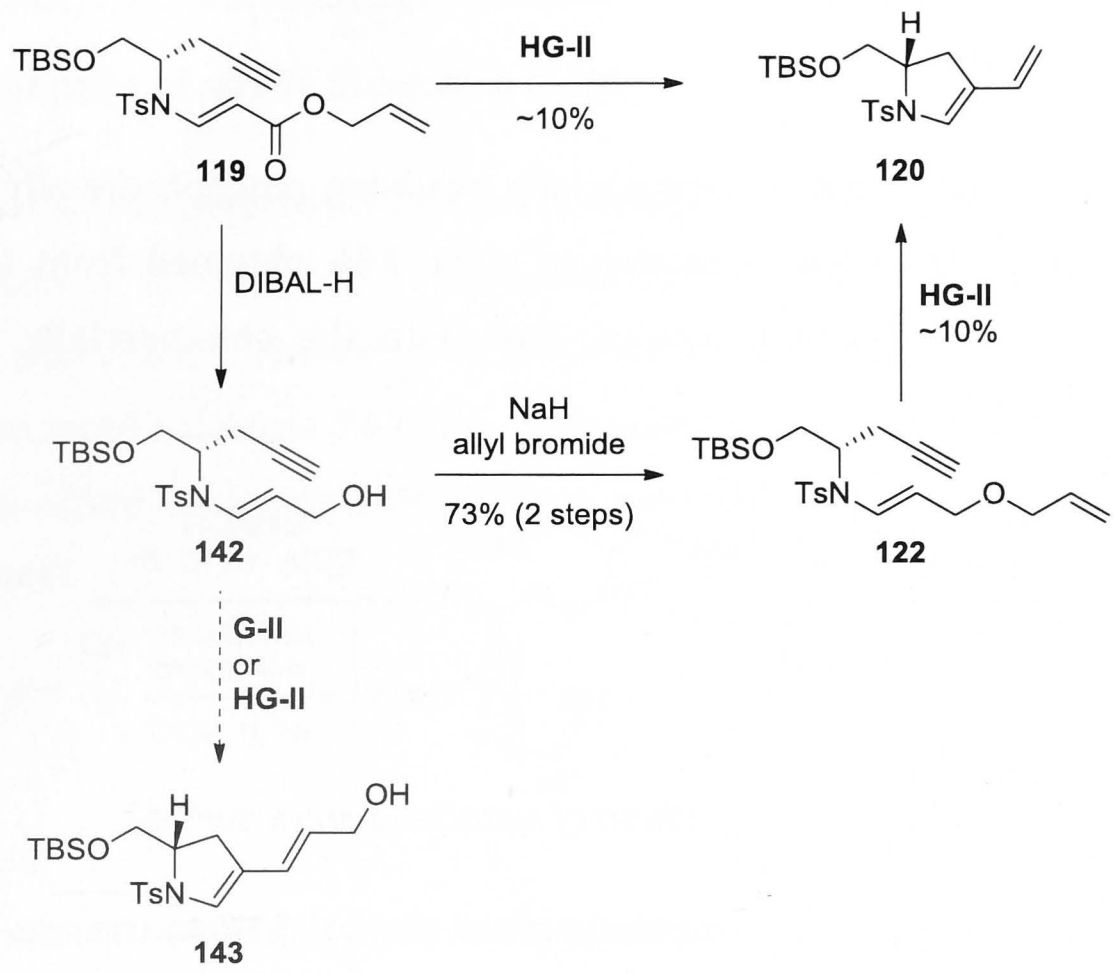
Scheme 3.2 *– Metathesis of 1,7-enynes*[55]

Entry	Substrate	R	Atm.	Time (h)	Product	Yield (%)
1	**140a**	H	Ar	41	**141a**	32
2	**140a**	H	Ethylene	1.5	**141a**	96
3	**140b**	OH	Ar	1.5	**141b**	>99
4	**140c**	OBn	Ar	41	**141c**	44
5	**140d**	OTBDPS	Ar	41	**141d**	7

Table 3.1 *– Conditions for the metathesis of 1,7-enynes*[55]

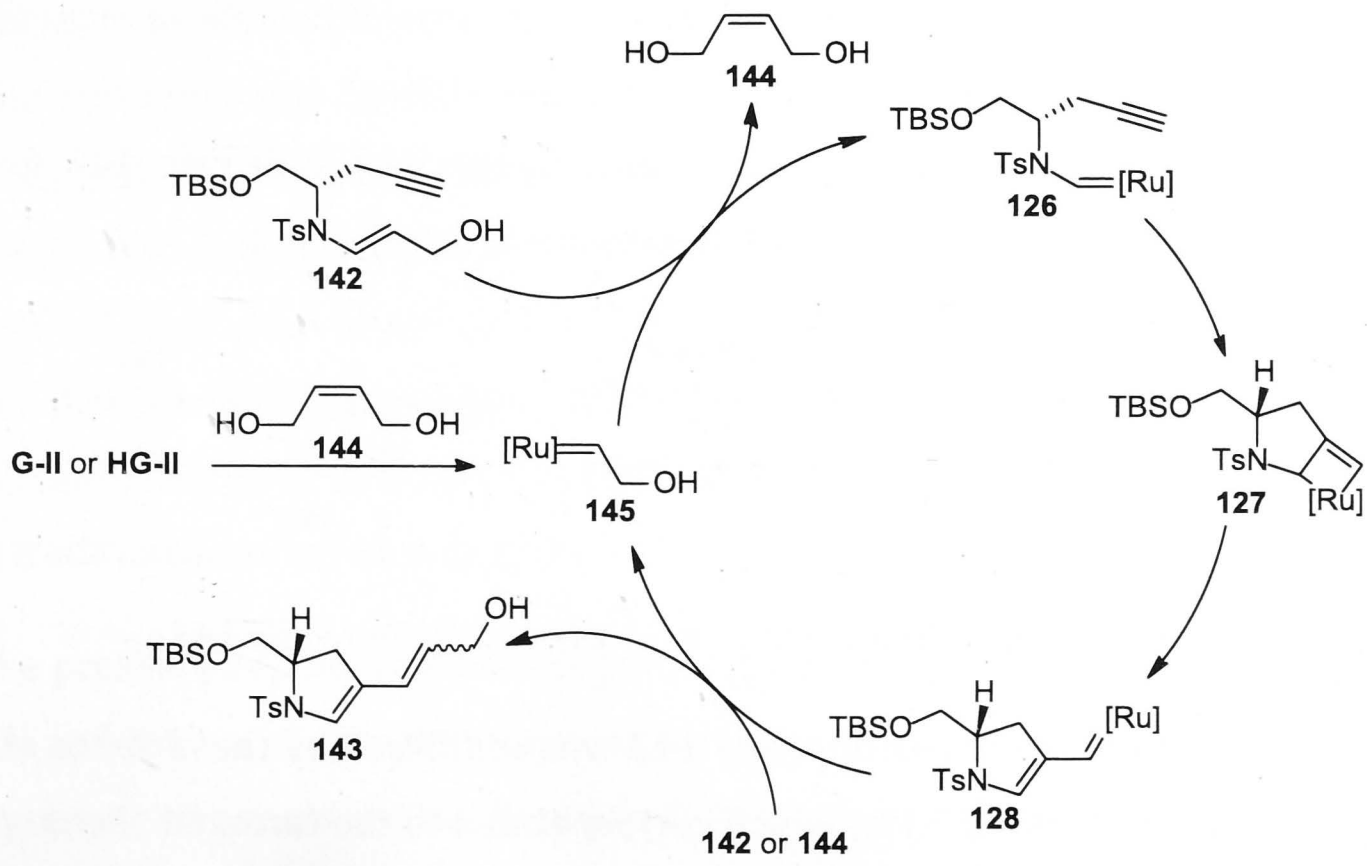
The evidence that allylic hydroxyl groups do enhance the rate of metathesis in the examples shown by Hoye and Imahori indicated that designing a new substrate which carries an allylic alcohol would be desirable.

Fortunately, in the synthesis of the allylic ether **122** from the allylic ester **119**, compound **142** bearing an allylic hydroxyl group had already been produced (Scheme 3.3). With this new substrate in hand, it was hoped that subjecting it to standard metathesis reaction protocols would yield the desired dihydropyrrole **143** with a handle to introduce the rest of the sidechain.



Scheme 3.3 – *New proposed enyne metathesis precursor*

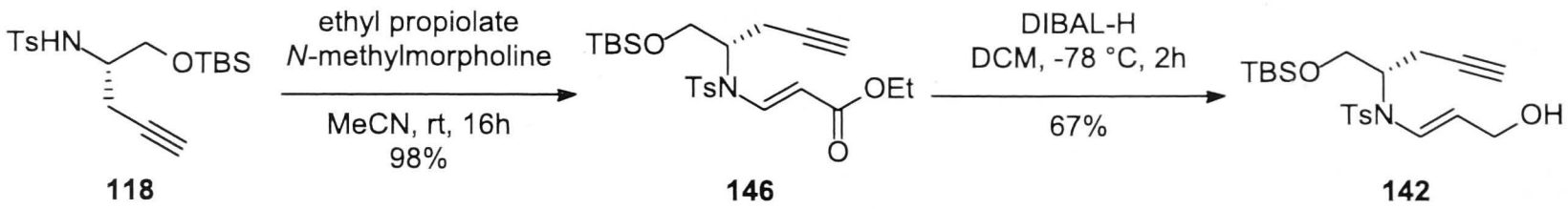
It is postulated that the mechanism by which the metathesis occurs (Scheme 3.4) would involve the loading of ruthenium onto the alkene to give ruthenium carbene **126** which would subsequently undergo a RCEYM to deliver vinyl carbene **128**. A final cross metathesis with an allylic alcohol, either from the substrate **142** or *cis*-but-2-ene 1,4-diol (**144**) would hopefully deliver dihydropyrrole **143** bearing a side chain which can be manipulated later in the synthesis. The employment of diol **144** as an additive would limit the possibility of obtaining products incorporating styrene-like units from **G-II** or **HG-II** in the final step as well as aid turnover of the catalyst due to the presence of an allylic alcohol.



Scheme 3.4 – *Catalytic cycle for metathesis of enyne **142***

3.2 Synthesis

As allyl propiolate is not a commercially available reagent, the allylic alcohol **142** was obtained instead from the reduction of ester **146** obtained from the aza-Michael addition of the protected amino alcohol **118** with the commercially available ethyl propiolate (Scheme 3.5).



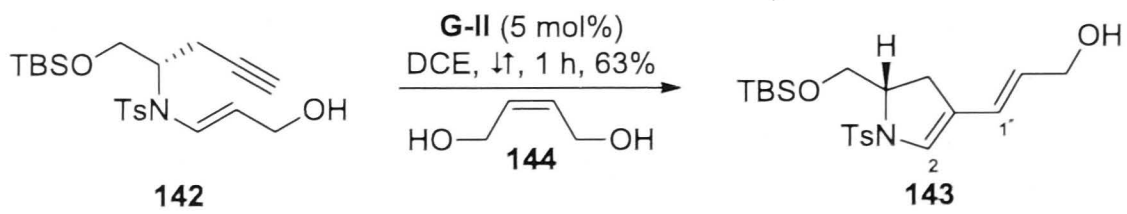
118 **146** **142**

Scheme 3.5 – *Synthesis of metathesis precursor* ***142***

The transformation of the protected amino alcohol **118** to the aza-Michael adduct **146** was confirmed by the observation of two mutually coupled resonances (J = 14.4 Hz) at δ 7.69 and δ 5.67 in the ^{1}H NMR spectrum, which corresponded to the newly installed *trans*-alkene in the latter, as well as the disappearance of a doublet at δ 4.92 (J = 8.4 Hz) which belonged to the amine proton in the former. The ^{13}C NMR spectrum displayed a new peak at δ 167.2 corresponding to the ester carbonyl group and the ESI mass spectrum displayed the sodium adduct at m/z 488.

The reduction of the ester **146** to the allylic alcohol **142** proceeded smoothly in the presence of DIBAL-H to provide the desired compound in moderate yield. The ^{13}C NMR spectrum of compound **142** lacked the resonance due to the ester carbonyl (as seen at δ 167.2 in the previous compound) and the ^{1}H NMR spectrum lacked the resonances attributed to the ethyl ester at δ 4.14 and δ 1.25 indicating that the ester functionality had been removed.

The metathesis rearrangement performed on the new substrate **142** fortunately provided the desired dihydropyrrole **143** in 63% yield (Scheme 3.6).



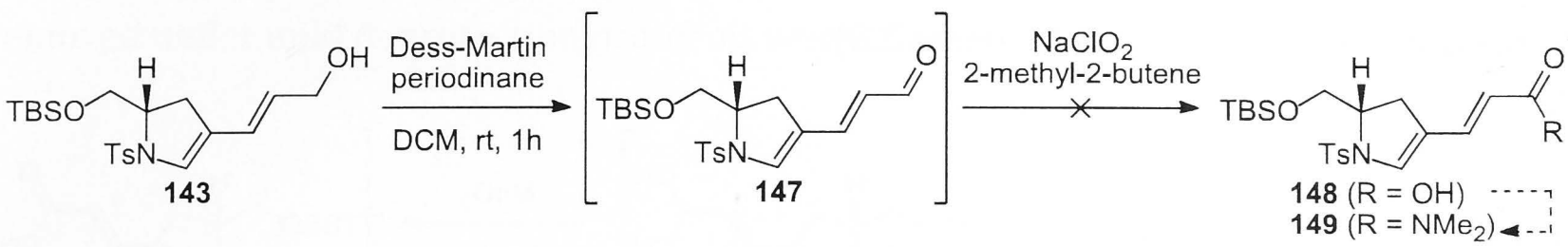
142 **143**

Scheme 3.6 – *Metathesis of enyne* ***142*** *to dihydropyrrole* ***143***

The formation of the dihydropyrrole **143** was confirmed by the absence of the one-proton triplet at δ 1.81 (J = 2.7 Hz) which corresponded to the terminal alkyne proton in enyne **142** and the appearance of a two-proton multiplet at δ 6.34 corresponding to the C2 and C1″ protons in the ^{1}H NMR spectrum.

3.2.1 Oxidation of allylic alcohol moiety

Following this success, methods were investigated for the manipulation of the allylic alcohol side chain to deliver a compound bearing a dimethyl acrylamide side chain as observed in porothramycin. The initial strategy involved the oxidation of the allylic alcohol **143** to the conjugated aldehyde **147** and subsequently to the conjugated acid **148**, which would hopefully afford the amide **149** when coupled with dimethylamine (Scheme 3.7).



Scheme 3.7 *– Attempted oxidation of allylic alcohol* ***143*** *to corresponding acid* via *aldehyde* ***147***

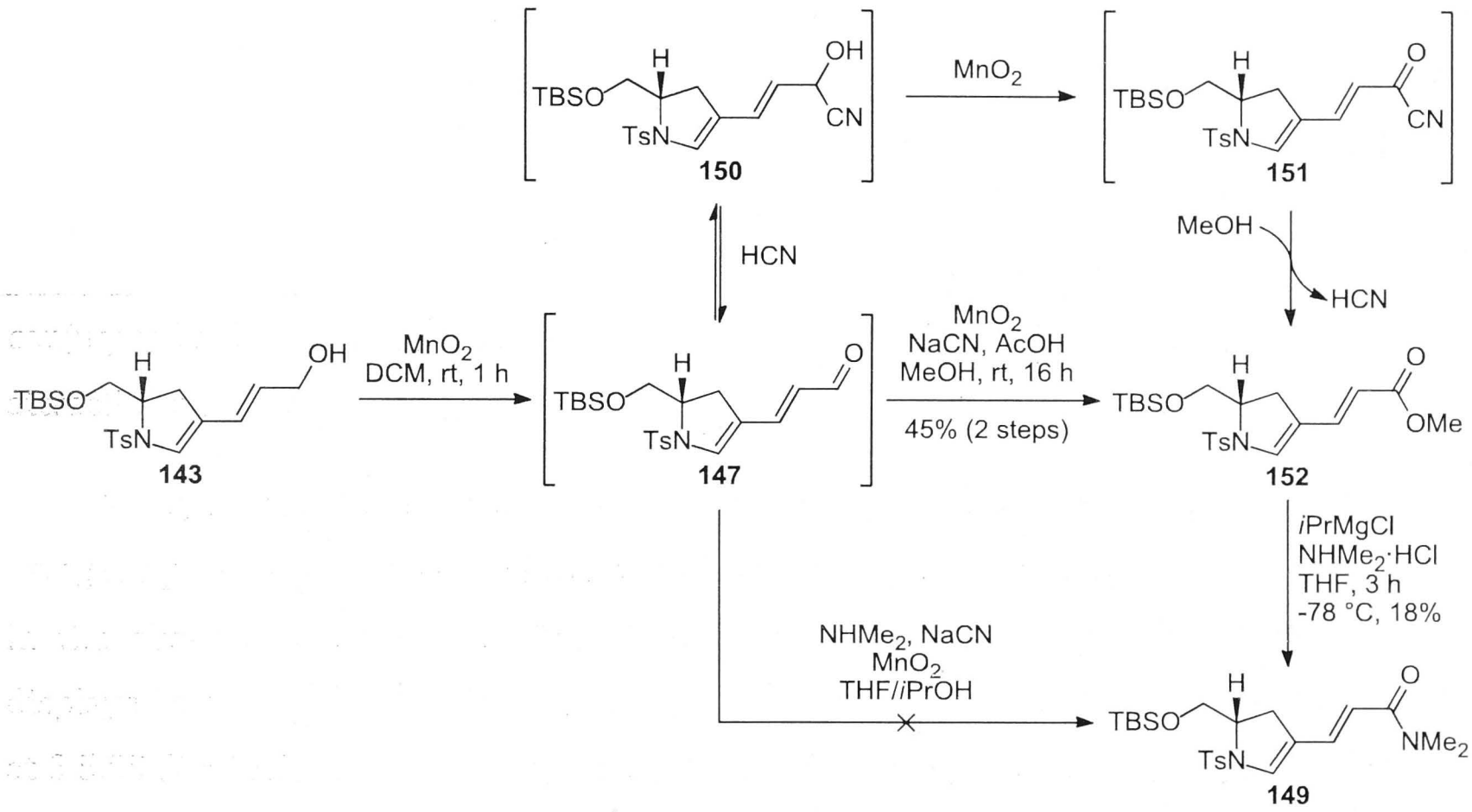
Oxidation of the allylic alcohol **142** to the aldehyde **147** proceeded smoothly in the presence of Dess-Martin periodinane (DMP) albeit with by-products which were not removed by additional purification steps due to possible instability of the aldehyde moiety (Scheme 3.7). The use of sodium hydrogencarbonate as a buffer in the DMP oxidation reaction did not deliver the aldehyde **147** in the absence of the aforementioned by-products and as such was omitted from further reactions. An oxidation of compound **147** so obtained from the DMP oxidation to the corresponding acid **148** under Pinnick conditions failed to deliver the desired product. The use of additives such as hydrogen peroxide, as described in a procedure reported by Dalcanale and Montonari,[56] also failed to give the acid **148** and this synthetic strategy was abandoned.

Attempts to obtain dimethyl amide **149** from aldehyde **147** using one-pot oxidative amidation protocols also failed.[57] While the protocols worked well to transform simple benzoic and allylic aldehyde substrates to various tertiary amides, the reactions, which employed *t*-butyl hydroperoxide as an oxidant or were catalysed by palladium, failed to transform aldehyde **147** to the desired amide **149**.[58,59] The review published by Ekoue-Kovi and Wolf in 2008 also covered other oxidative methods, however, due to lack of material, these reactions were not investigated and efforts were focussed towards the use of more traditional oxidation sequences.[56,57]

The presence of impurities accompanying the aldehyde **147** obtained from the DMP oxidation and the possibility that these by-products were interfering with the subsequent oxidation processes could not be discounted. As a result, a cleaner oxidation was required and attention was turned towards to the oxidation of allylic alcohols using activated manganese dioxide.[60] The possibility of extending this protocol to the oxidation of the

conjugated aldehyde to esters and amides in the presence of sodium cyanide made this an attractive alternative to the previous protocol.[61,62]

Thus, the oxidation of the allylic alcohol with activated manganese dioxide, prepared using the protocol described by Attenburrow and co-workers,[63] afforded the aldehyde **147** in the absence of impurities. The ^{1}H NMR spectrum of the crude reaction mixture displayed a one proton doublet at δ 9.52 (J = 7.8 Hz) and a one-proton doublet of doublets at δ 5.85 (J = 15.3, 7.8 Hz) corresponding to the aldehyde proton and the proton attached to the α-carbon, respectively (Scheme 3.8).



Scheme 3.8 *– Oxidation of allylic alcohol* ***143*** *with manganese dioxide*

The oxidation of the aldehyde **147** directly to the dimethyl amide **149** was met with difficulties, which were attributed to the purity of the dimethylamine solution employed.[62] Due to the lack of material, this strategy was abandoned and the aldehyde **147** was oxidised to the methyl ester **152**, by way of the formation of the cyanohydrin **150** and acyl cyanide **151**, after exposure to manganese dioxide, sodium cyanide and methanol to deliver the desired compound in a moderate yield over 2 steps (Scheme 3.8).[61] The installation of the methyl ester was confirmed by the disappearance of the one-proton doublet at δ 9.52 (J = 7.8 Hz) and the presence of a three-proton singlet at δ 3.72 in the ^{1}H NMR spectrum and the observation of ions corresponding to the proton adduct and sodium adduct at m/z 452 and 474, respectively, in the ESI mass spectrum.

An attempt to introduce the dimethyl amide group using isopropylmagnesium chloride and dimethylamine hydrochloride delivered the desired compound **149** in a low and unoptimised 18% yield (Scheme 3.8). The ^{1}H NMR spectrum of this compound

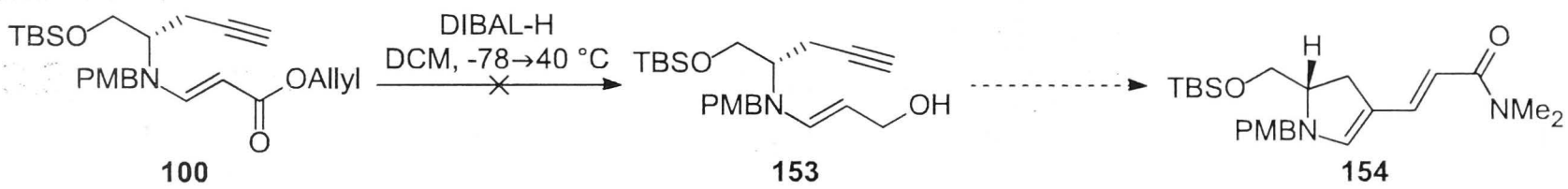
displayed two three-proton singlets at δ 3.04 and δ 3.00 which were indicative of the presence of a dimethyl amide and the ESI mass spectrum displayed ions associated with the proton adduct and sodium adduct at *m/z* 465 and 487, respectively.

With the completed C-ring and side chain in hand, attempts were made to deprotect the fully synthesised C-ring using sodium/naphthalene and samarium diiodide,[64] however, due to a lack of material and the degradation of the material due to the aforementioned reaction conditions, alternate commercially available protecting groups which could be removed under mild deprotection protocols were trialled.

3.3 Investigation with alternate protecting groups

3.3.1 Revisiting PMB

Having concluded that the presence of an allylic alcohol promoted the desired metathesis reaction, the previously prepared PMB protected conjugated ester **100** was subject to reduction conditions in order to investigate the effect of an electron donating protecting group on the reaction. Unfortunately, the reduction of ester **100** to allylic alcohol **153** was found to not proceed even after warming of the reaction mixture (Scheme 3.9). Once again, the electron donating protecting group may be the reason for the difficulty in accessing the desired allylic alcohol due to the decreased electrophilicity of ester moiety. Further, given the possible instability of the enamine moiety and the potential for reduction of the enamine unsaturation, this avenue was not further explored.



Scheme 3.9 *– Attempted synthesis of PMB protected metathesis precursor* ***153***

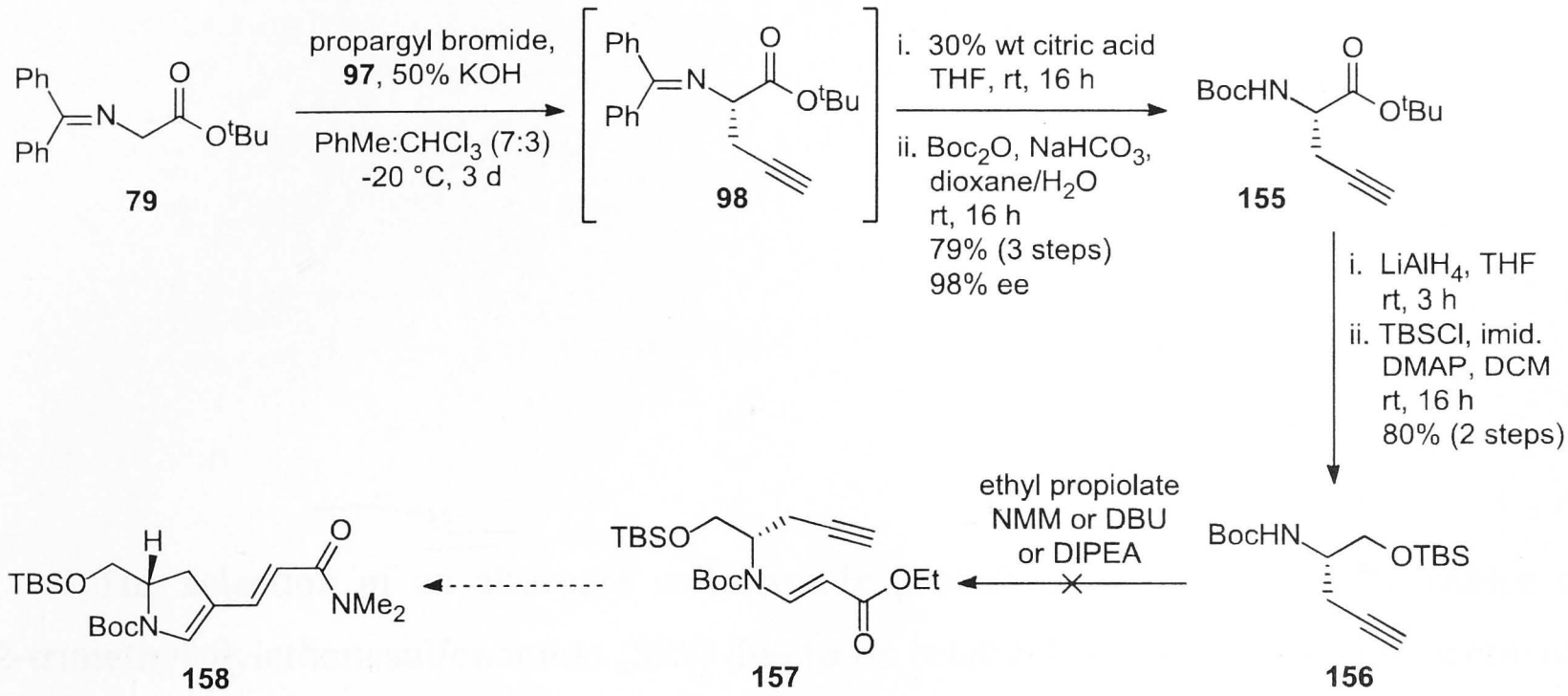
3.3.2 Alternate electron withdrawing protecting groups – carbamates

The lack of success when employing PMB indicated that the use of an electron withdrawing group was likely more desirable. Thus, the Boc protecting group was trialled.

The synthesis of the protected amino alcohol **156** proceeded smoothly under previously described protocols however, the aza-Michael addition between this compound and ethyl propiolate to deliver the conjugated ester **157** was observed to not proceed (Scheme 3.10). A literature search revealed that an aza-Michael addition between a carbamate and a propiolate has not been observed and only one reaction of a similar nature between an oxazolidinone and ethyl propiolate has been reported.[65]

It was postulated that due to the comparatively higher pK_a of a proton attached to a carbamate (pK_a = 24.8 for primary ethyl carbamate)[66] than one attached to a sulfonamide (pK_a = 16.1 for primary benzenesulfonamide)[67], the base employed was not sufficiently basic for this reaction. As such, the use of other organic bases such as DBU and Hunig's base were trialled, however under these conditions, the reaction was also observed to not proceed. In light of this, the reaction was also attempted with potassium

hexamethyldisilazide (KHMDS) ranging from 0.1-1.0 equivalents in an attempt to deprotonate the carbamate before addition of the ethyl propiolate, however, all reactions to this end also failed and the employment of a carbamate protecting group was abandoned.



Scheme 3.10 *– Attempted synthesis of Boc protected metathesis precursor*

Whilst compound **157** has been previously synthesised in the group and subjected to the metathesis rearrangement (Section 1.5.2), the route by which compound **157** was obtained contained low yielding steps.[42] The low yield was due to the aza-Michael addition of ethyl propiolate and the primary amine derivative of compound **156** which led to the formation of *E:Z* isomers in a ~1:1 ratio. With the product in hand, the Boc protection to give compound 157 only proceeded with the *E*-isomer, thus resulting in a low yield. Although the described synthetic procedure previously used within the group was not employed to obtain compound **157**, an analogous reaction involving the aza-Michael addition of the primary amino ester derivative of compound **155** to ethyl propiolate was carried out, however, all efforts to this end were unsuccessful in delivering the desired product.

3.4 Conclusion

The new metathesis strategy involving the use of an allylic alcohol group to promote the desired metathesis reaction proceeded smoothly and the investigation into the manipulation of the resulting allylic alcohol group to the desired side chain as observed in porothramycin (**2**) has yielded promising results.

Due to the use of the tosyl protecting group, which has been known to be difficult to remove, an investigation into the use of alternate non-sulfonamide protecting groups was undertaken. Unfortunately, this proved unsuccessful and as such, attention was turned to

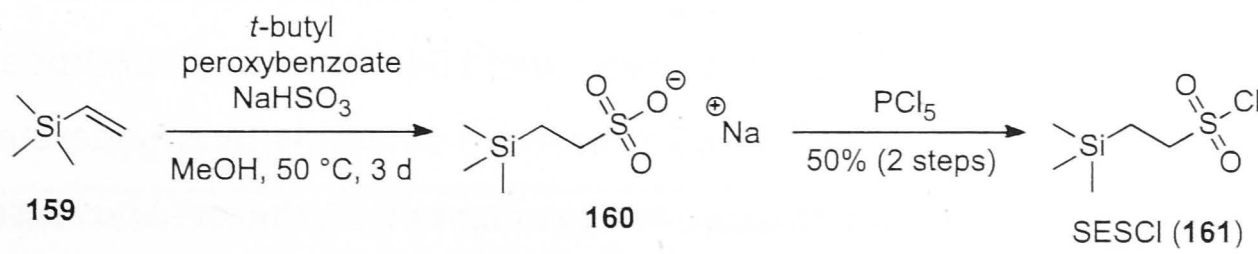
the use of a sulfonamide protecting group offering similar electronic properties while also carrying the ability to be removed under mild conditions.

Chapter 4 Towards the synthesis of porothramycin

The selection of an alternate sulfonamide protecting group led to the choice of 2-trimethylsilylethanesulfonamide (SES) due to its relatively mild deprotection protocols involving removal in the presence of fluoride ions. Although it had been employed previously within the group (Section 1.5.2), the use of this protecting group during the development of a suitable metathesis protocol was not initially pursued as it was not readily available.

4.1 Synthesis

Before the synthesis of the substrate could begin, the synthesis of 2-trimethylsilylethansulfonyl chloride (SESCl) was undertaken. Vinyltrimethylsilane **159** was either obtained commercially or from the addition of vinyl magnesisum bromide to chlorotrimethylsilane.[68] With compound **159** in hand, it then underwent addition of sodium hydrogensulfite in the presence of *tert*-butyl peroxybenzoate to give sulfonate **160** which was chlorinated with phosphorus pentachloride to give the desired sulfonyl chloride **161** in 50% yield over two steps (Scheme 4.1).[69,70]

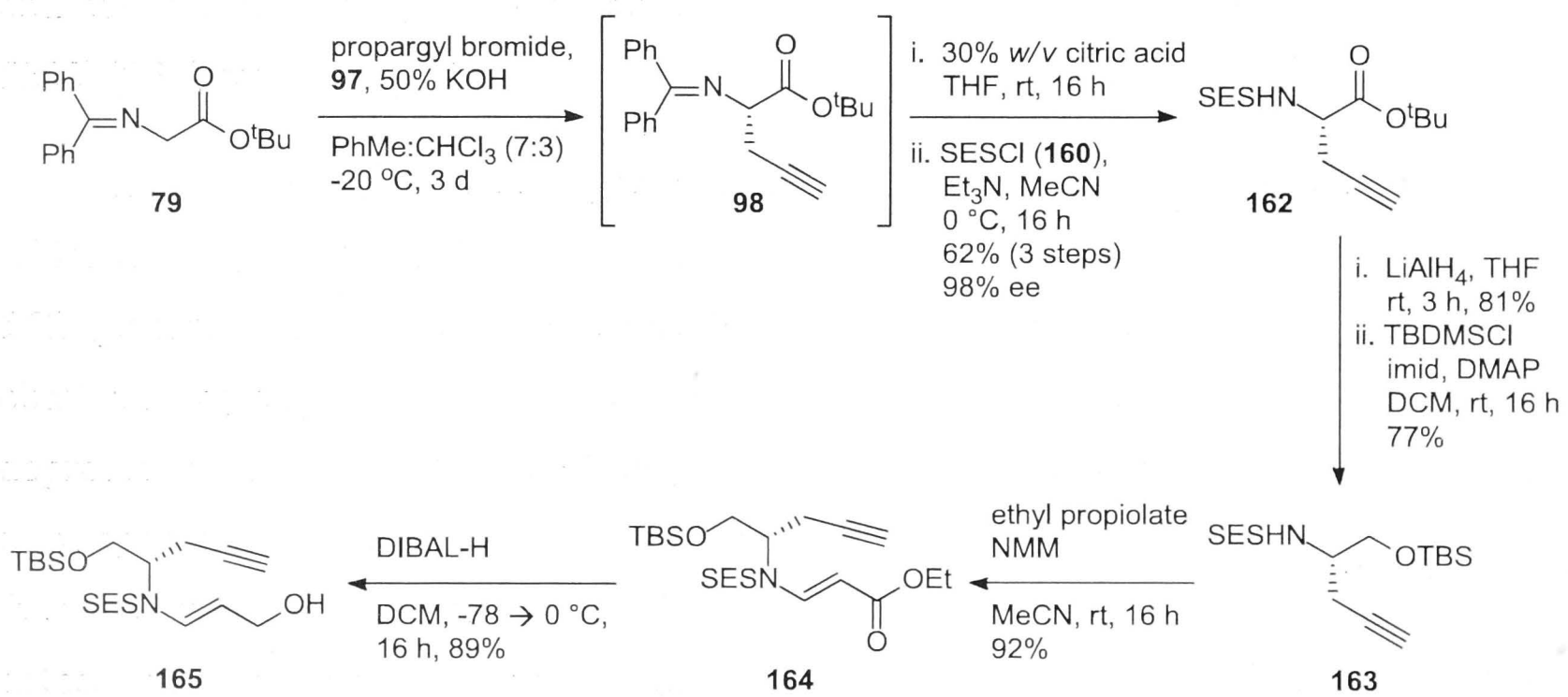


***Scheme 4.1** – Synthesis of SESCl (**161**)*

The disadvantages of this protecting group included decomposition over time and as such, the reagent was synthesised when needed. Some problems were encountered during

the chlorination of the sulfonate with thionyl chloride, as described by Weinreb and co-workers in 1998,[69] and it was found that following an earlier procedure in which Weinreb and co-workers employed phosphorus pentachloride was more successful in delivering SESCl (**161**) consistently.[70]

The synthesis once again began with the asymmetric alkylation of glycine imine **79**, which was deprotected and protected using SESCl (**161**) to provide protected amino ester **162** (Scheme 4.2). The *ee* was determined by analysis of Boc ester **155**, which was obtained by protecting an aliquot of the compound obtained after diphenylmethylidene deprotection with Boc anhydride. This process was deemed necessary as extensive studies into separation and identification of the enantiomers of amino ester **162** using chiral HPLC failed to provide suitable protocols. This failure may be attributed to the inability of the detection devices used to observe the SES protected amino ester **162** in an appropriate UV range and to detect any significant rotations due to the lower $[\alpha]_D$ value for compound **162** $\{[\alpha]_D^{20}$ +6.1 (*c* 0.98, $CHCl_3$)$\}$, in comparison to Boc protected amino ester **155** $\{[\alpha]_D^{20}$ +33.6 (*c* 0.63, $CHCl_3$)$\}$.

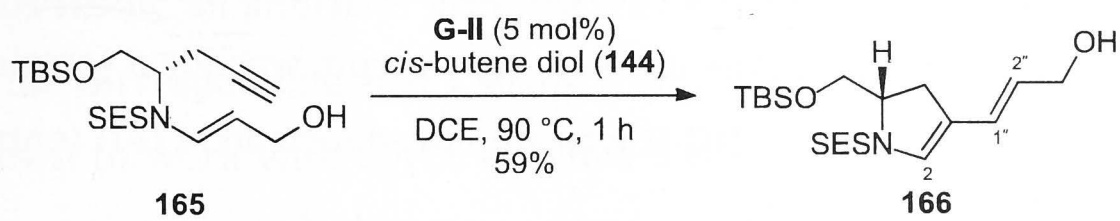


Scheme 4.2 *– Synthesis of SES protected metathesis precursor* ***165***

The ester functionality was reduced and the corresponding primary alcohol was protected as the TBS ether **163** (Scheme 4.2). The aza-Michael addition of ethyl propiolate proceeded smoothly to deliver the conjugated ester **164**. The initial attempt at reduction of the ester **164** to the allylic alcohol **165** proceeded smoothly in a moderate 70% yield however, by allowing the reaction mixture to warm up to 0 °C, the yield increased to 89%.

4.1.1 Metathesis

With the allylic alcohol **165** in hand, the compound was subjected to same conditions employed for the tosyl derivative – Grubbs' 2nd generation catalyst (**G-II**) in the presence of *cis*-butene diol (**144**) – to deliver the dihydropyrrole **166** in 59% yield (Scheme 4.3). The ^{1}H NMR spectrum of this compound displayed a one-proton singlet at δ 6.21 corresponding to the proton attached to C2. It also exhibited a pair of mutually coupled resonances at δ 6.31 (J = 15.6 Hz) and δ 5.57 (J = 15.6, 5.6 Hz), which are attributed to the protons at C1″ and C2″ respectively, and indicate that alkene is in a *trans*-configuration. In addition, the ^{1}H NMR lacked the triplet at δ 2.02 attributed to the alkynyl proton in compound 165.



165 166

Scheme 4.3 *– Metathesis of enyne* ***165*** *to dihydropyrrole* ***166***

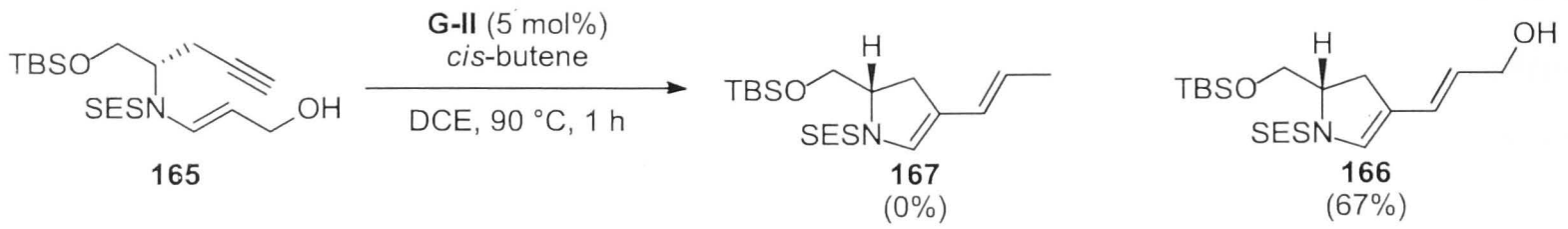
Optimisation of the reaction conditions was undertaken to provide a greater yield of the desired compound (Table 4.1). The table indicates that by changing the catalyst from **G-II** to **HG-II** reduced the reaction time significantly and as such, further reactions were performed using **HG-II** as the catalyst. The catalyst loading was also investigated and it was found that increasing the loading gave improved yields, however, further reactions were carried out using 5 mol% loading as the advantage in using 10 mol% loading was not great (entries 2-4).

Entry	Catalyst (mol%)	Additive	Time (min)	Isolated Yield (%)
1	**G-II** (5.0)	*cis*-butene diol (5.0 eq)	60	59
2	**HG-II** (2.5)	*cis*-butene diol (5.0 eq)	15	55
3	**HG-II** (5.0)	*cis*-butene diol (5.0 eq)	15	77
4	**HG-II** (10.0)	*cis*-butene diol (5.0 eq)	15	82
5	**HG-II** (5.0)	*cis*-butene (atmosphere)	15	67
6	**HG-II** (5.0)	-	10	81-quant.

Table 4.1 *– Conditions for optimisation of metathesis of enyne* ***165*** *to dihydropyrrole* ***166***

The use of a *cis*-butene atmosphere was trialled in an attempt to produce conjugated compound **167** bearing the side-chain observed in sibiromycin (**3**) however, this proved unsuccessful and delivered the conjugated alcohol **166** as the sole product (entry 5) (Scheme 4.4). This result prompted the move towards an additive free metathesis which

delivered yields ranging from 81% to quantitative during the initial optimisation studies (entry 6).



Scheme 4.4 *– Attempted metathesis of enyne* ***165*** *to diene* ***167*** *with* cis-*butene*

Unfortunately, after optimisation and over the course of the project, yields ranging from 50-60% were consistently obtained despite the use of fresh catalyst either with or without distilled *cis*-butene diol. In light of this, a second attempt at optimisation was undertaken employing allyl alcohol as the additive (Table 4.2). The amount of allyl alcohol was varied and it was found that the use of 2 equivalents was ideal (entries 1-4) and the yield obtained was mirrored when **HG-II** was employed instead of **G-II** (entry 5).

Entry	Catalyst (mol%)	Additive	Time (min)	Isolated Yield (%)
1	**G-II** (5.0)	allyl alcohol (1.0 eq)	60	66
2	**G-II** (5.0)	allyl alcohol (2.0 eq)	60	75
3	**G-II** (5.0)	allyl alcohol (3.0 eq)	60	59
4	**G-II** (5.0)	allyl alcohol (5.0 eq)	60	51
5	**HG-II** (5.0)	allyl alcohol (2.0 eq)	60	71

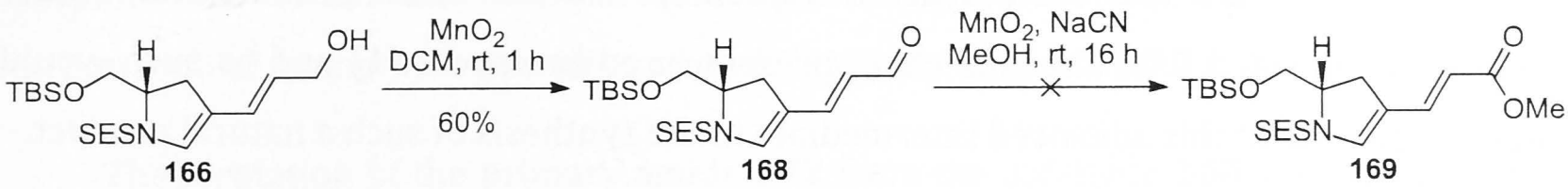
Table 4.2 *– Conditions for optimisation of metathesis of enyne* ***165*** *to dihydropyrrole* ***166***

4.1.2 Oxidation of allylic alcohol moiety

After obtaining the desired dihydropyrrole **166**, attention was turned to the oxidation of the allylic alcohol functionality to the methyl ester **169** as described in the protocol developed for the tosyl derivative (Section 3.2.1). Following the described procedure,[63] a sluggish conversion to the aldehyde **168** was observed and it was clear that the reactivity of the SES derivative was comparatively less than that of the tosyl derivative. In light of this, the reaction was heated to reflux and the aldehyde **168** was obtained in 60% isolated yield (Scheme 4.5).

The formation of compound **168** was confirmed by the ^{1}H NMR spectrum which displayed a pair of mutually coupled resonances in the form of a distinctive one proton doublet at δ 9.54 (J = 8.0 Hz) and a doublet of doublets at δ 5.93 (J = 15.2, 7.6 Hz) corresponding to the protons attached to the carbonyl and α-carbon respectively. The ^{13}C

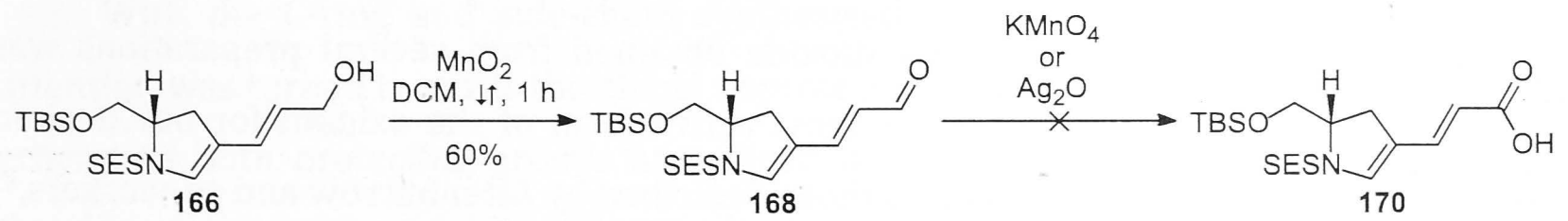
NMR spectrum also displayed a peak at δ 193.2 corresponding to the newly installed aldehyde and the IR spectrum lacked the OH stretch seen at 3431 cm^{-1} in the precursor.



Scheme 4.5 *– Attempted oxidation of allylic alcohol* ***166*** *to methyl ester* ***169*** via *aldehyde* ***168***

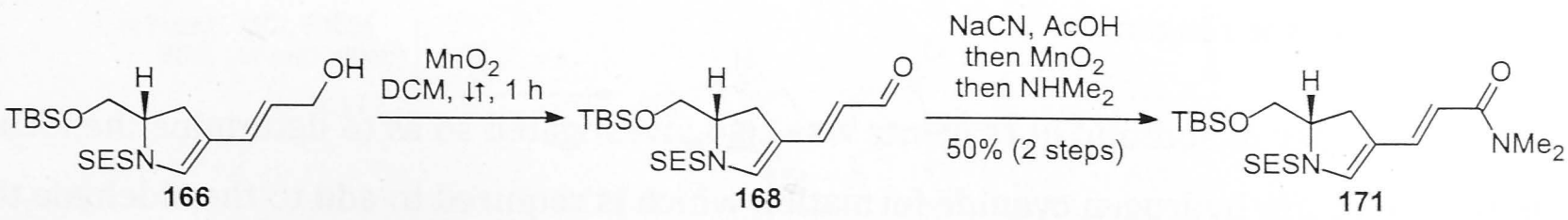
Unfortunately, repeated attempts at the subsequent oxidation to the ester **169** were unsuccessful; once again demonstrating the contrast in reactivity of the SES and tosyl derivatives.

Due to this result, an alternate protocol was sought and the oxidation of the allylic alcohol **166** to the corresponding acid **170**, by way of the aldehyde **168**. Several oxidation procedures known to work with allylic alcohols including potassium permanganate and silver oxide were attempted, however, the results were inconclusive and often decomposition of the starting material was observed (Scheme 4.6).[61,71] Oxidation protocols involving acidic reagents such as the Jones' oxidation were not investigated due to the acidic nature of the reagent and known difficulties involving *in situ* deprotection and oxidation of TBS ethers.[72] The lack of success associated with this strategy led to further investigation of the reaction involving manganese dioxide.



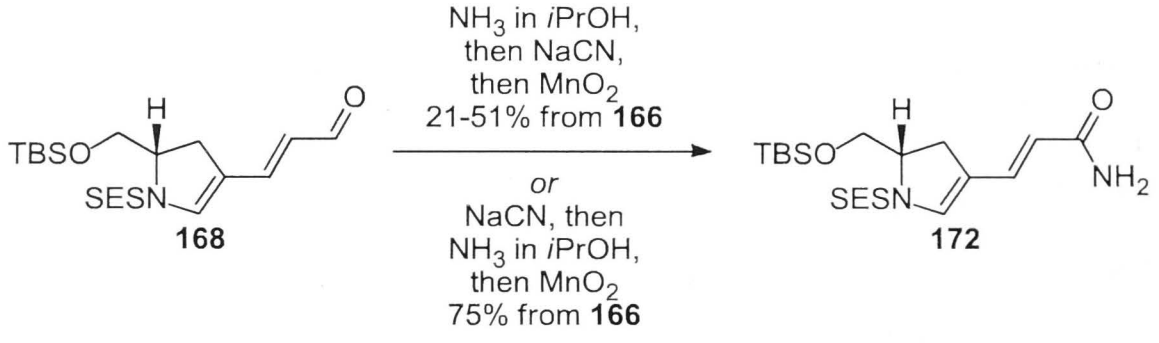
Scheme 4.6 *– Attempted oxidation of allylic alcohol* ***166*** *to corresponding acid* via *aldehyde* ***168***

Attempts were made towards the direct synthesis of dimethyl amide **171** from the aldehyde **168** and initial results delivered the desired compound **171** in moderate yields (Scheme 4.7). However, difficulties experienced in reproducing the result despite extensive optimisation – involving the use of fresh manganese dioxide, finely ground sodium cyanide, freshly distilled acetic acid and performing the reaction in a variety of solvents – and the deteriotation of the dimethylamine solution over a short period of time rendered this approach nonviable.



Scheme 4.7 *–Oxidation of allylic alcohol* ***166*** *to dimethylamide* ***171*** via *aldehyde* ***168***

Given the successful oxidation of aldehyde **168** in the presence of dimethylamine, albeit irreproducible, the use of ammonia in the oxidation of the compound **168** to the primary amide **172** was trialled (Scheme 4.8). The production of the primary amide side-chain also coincided with the side-chain present in anthramycin (**1**) and as such would allow for the use of this advanced intermediate in the synthesis of such a natural product.



Scheme 4.8** – Attempted oxidation of aldehyde **168** to primary amide **171

Following a procedure reported by Gilman,[62] ammonia was introduced into the system by way of a saturated isopropanol solution and initial attempts at the conversion consistently delivered the amide **172** in yields ranging from 21-51% (Scheme 4.8). Attempts to improve the yield by employing an aprotic solvent such as tetrahydrofuran or 1,4-dioxane were unsuccessful due to the limited solubility of ammonia in such solvents. Other protic solvents such as methanol and ethanol were not trialled as they have been known to compete with ammonia and form the methyl and ethyl ester products respectively.[61,62]

An investigation of manganese dioxide obtained from several preparations was undertaken in order to determine the most active form of the oxidant for our desired reaction.[73] Various procedures, such as those described by Attenburrow and co-workers,[63] Ball and co-workers,[74] and Carpino,[75] were employed to generate activated manganese dioxide and the reaction times and yields obtained in all cases were similar indicating that the method by which the manganese dioxide was produced did not have a significant influence on the activity.

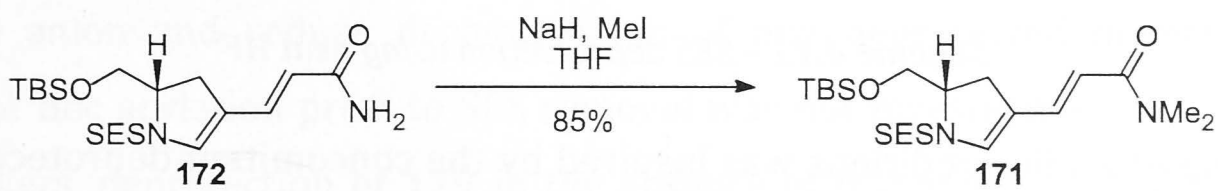
The major factor which influenced the activity of the manganese dioxide was time, as over the period of months reaction times increased and the equivalents of manganese dioxide required to push the reaction to completion also increased indicating a decrease in reactivity. As a result, the method reported by Carpino where manganese dioxide is obtained by addition of activated charcoal was employed due to ease of preparation and purification of the reagent.

The order of addition of reagents was also investigated so as to determine the ideal method of *in situ* hydrogen cyanide formation which is required to add to the aldehyde to

deliver a cyanohydrin species. This cyanohydrin is subsequently oxidised to the acyl cyanide and displacement by ammonia to deliver the desired primary amide. During this study, it was found that addition of sodium cyanide to isopropanol prior to the introduction of ammonia led to an improved 75% yield of amide **172** (Scheme 4.8).

The formation of the primary amide **172** from the aldehyde **168** was confirmed by the absence of the one proton doublet at δ 9.54 (J = 8.0 Hz) and the observation of a broad singlet at δ 5.48 corresponding to the amide protons on the ^{1}H NMR spectrum, whilst the ESI$^+$ mass spectrum displayed an ion corresponding to the sodium adduct at m/z 469.

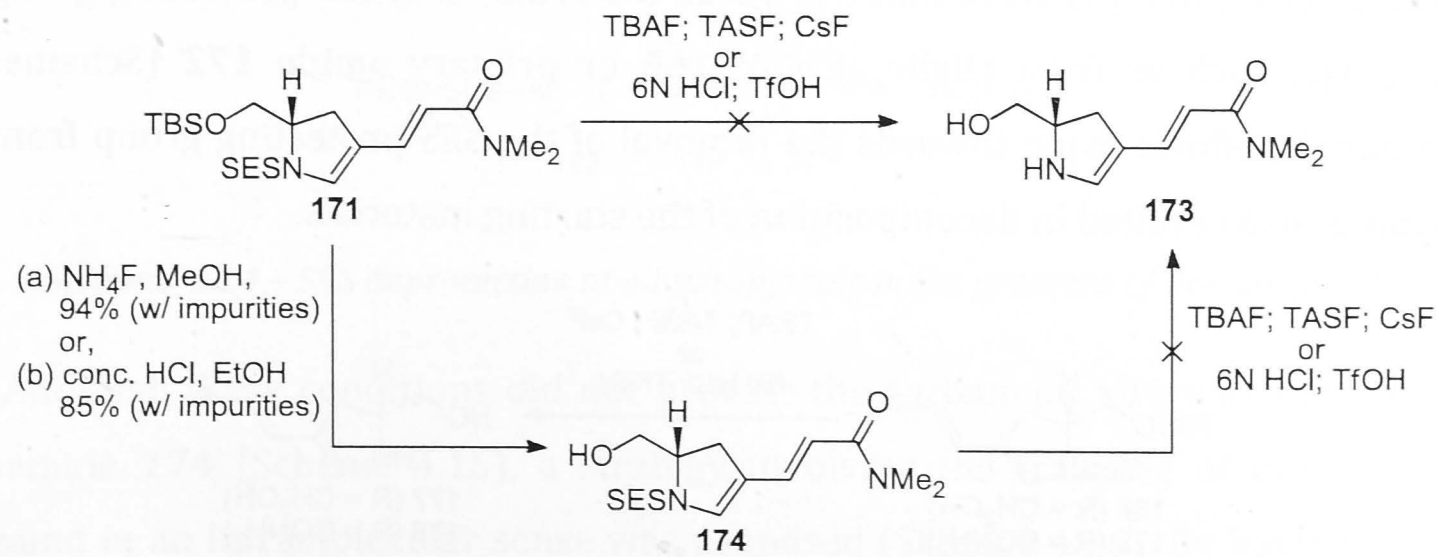
The primary amide **172** was subsequently methylated to deliver the dimethylamide **171** in good yield (Scheme 4.9) and the ^{1}H NMR spectrum of this compound showed two distinct three-proton singlets at δ 3.01 and δ 3.08 corresponding to the newly installed *N*-methyl groups.



Scheme 4.9 *– Methylation of primary amide* ***172***

4.1.3 SES deprotection

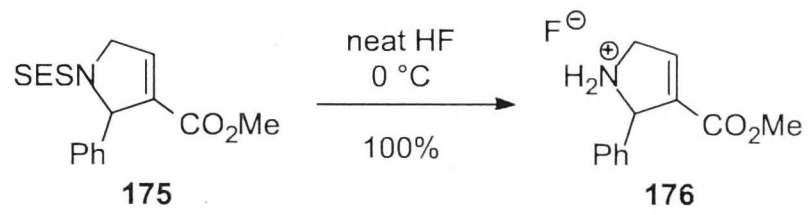
With the C-ring and side-chain synthesised in the form of dimethylamide **171**, attention was turned towards the global deprotection of the SES sulfonamide and the TBS ether. As both protecting groups are silicon based, it was believed that the use of a fluoride source such as tetrabutylammonium fluoride (TBAF) or cesium fluoride would deliver the unprotected dihydropyrrole **173**.[76] Unfortunately, under these conditions and other conditions reported for the deprotection of the SES protecting group,[77-81] the removal of the SES protecting group proved unsuccessful and either only TBS deprotection or decomposition was observed (Scheme 4.10).



Scheme 4.10 *– Attempted deprotection of compound* ***171***

The use of fluoride sources, namely tetrabutylammonium fluoride (TBAF), tris(dimethylamino)sulfonium difluorotrimethyl silicate (TASF) and cesium fluoride (CsF), led to decomposition of the starting material with no observation of any deprotected material.

The use of HF for the deprotection of this material was not trialled as research presented by Declerck and co-workers indicated that using HF·pyridine or HF in H_2O for the deprotection of dihydropyrrole **175** led to no reaction.[82] They did report the removal of the SES protecting group from compound **175** in the presence of neat HF, however due to safety concerns, this particular reaction was not performed (Scheme 4.11).



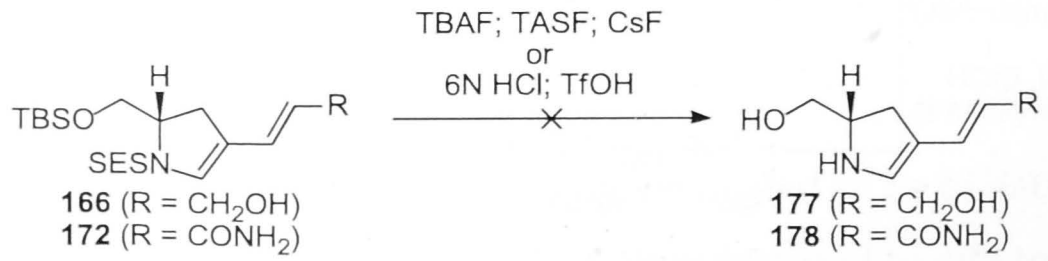
175 176

Scheme 4.11 *– SES deprotection using neat HF*

The use of acidic conditions was inspired by the concomitant deprotection of a Boc and a SES group on the same amine in refluxing 6 N HCl by Decicco and Grover as well was the SES deprotection of pipecolic derivatives by Varray and co-workers.[83,84] Unfortunately, the use of acid for the deprotection of compound **171** also led to decomposition (Scheme 4.10).

In light of this, milder conditions generally associated with the removal of silyl ethers such as ammonium fluoride or concentrated HCl in ethanol were trialled and yielded only the TBS deprotected compound **174** in good yields albeit in the presence of some impurities derived from the removed TBS group (Scheme 4.10). Further attempts to deprotect this material using the fluoride sources or acid conditions mentioned above once again resulted in decomposition.[77-80,82]

Due to the difficulties encountered in the removal of the SES protecting group from compound **171**, attempts were made towards the removal of the protecting group at an earlier stage, such as from allylic alcohol **166** or primary amide **172** (Scheme 4.12). Unfortunately, efforts made towards the removal of the SES protecting group from these compounds also resulted in decomposition of the starting materials.

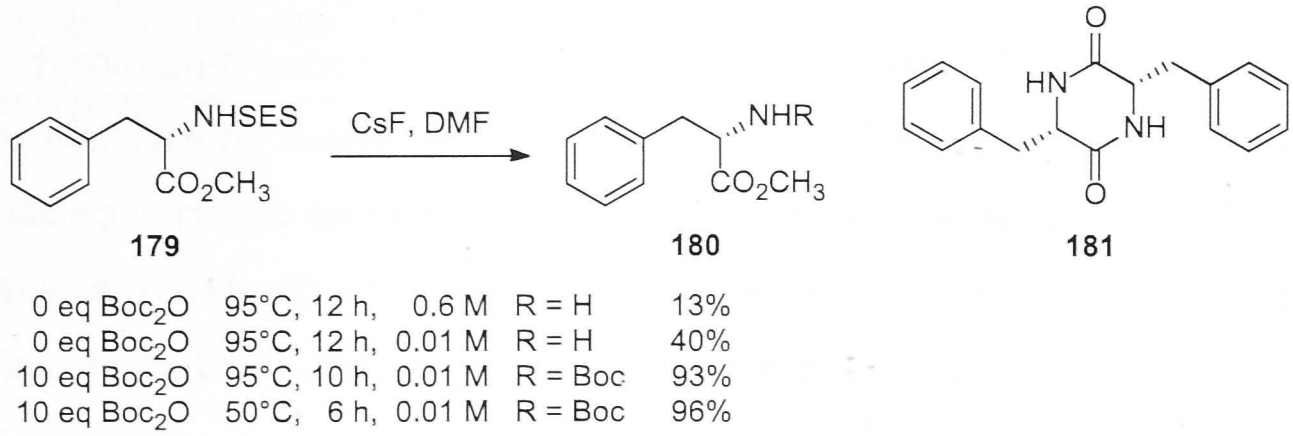


Scheme 4.12 *– Attempted deprotection at earlier stages (allylic alcohol **166** and primary amide **172**)*

The failure associated with the removal of the protecting group and the ability to obtain compound **173** may be due to the resulting amide anion or amine moiety participating in unwanted side reactions, such as aza-Michael additions. Thus, further investigation into alternate methods for removal of the SES protecting group and the use of additives with traditional SES removal conditions was undertaken.

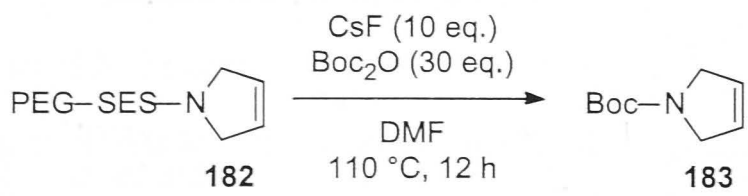
4.1.3.1 Alternate strategy for SES deprotection

In the search for alternative deprotection protocols, a procedure reported by Boger and co-workers demonstrated that Boc anhydride could be employed to trap the deprotected material as the carbamate **180** (Scheme 4.13).[78] The results indicated that dilute solutions were ideal and the nitrogen anion derived from the SES deprotection may be unstable thus allowing the presence of an electrophile such as the Boc protecting group to trap the anion and reduce decomposition of any deprotected material. Although possibility of Boc acylation prior to SES removal was not investigated in detail by Boger and co-workers, deprotection of **179** in the absence of Boc anhydride led to substantial amounts of the corresponding diketopiperazine **181**.



Scheme 4.13 *– SES deprotection in the presence of Boc anhydride*

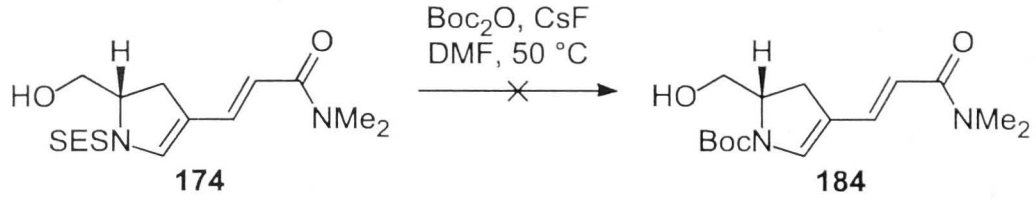
This protocol was also employed by Varray and co-workers for the deprotection of dihydropyrrole **182** to give the Boc protected derivative **183** (Scheme 4.14).[84]



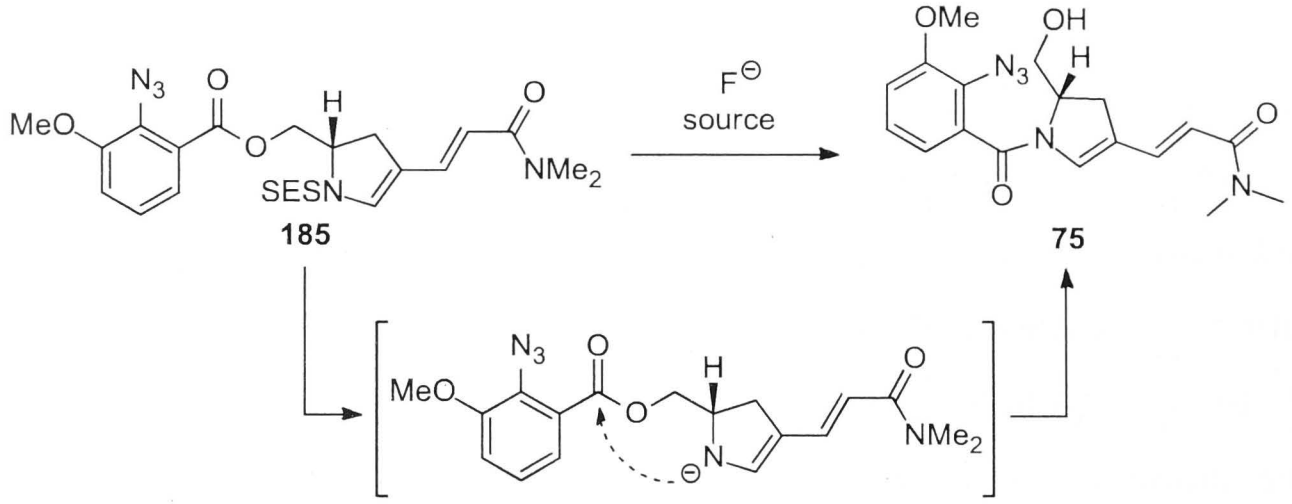
Scheme 4.14 *– SES deprotection of dihydropyrrole in the presence of Boc anhydride*

Although these conditions did not provide the carbamate **184** when attempted on sulfonamide **174** (Scheme 4.15), a strategy involving the trapping of the deprotected compound in an intramolecular sense was proposed (Scheme 4.16). By having the A-ring installed as an ester **185**, it was anticipated that the nitrogen anion so formed under SES

deprotection conditions would participate in an intramolecular nucleophilic substitution reaction at the ester carbonyl and lead to the formation of the amide **75**.

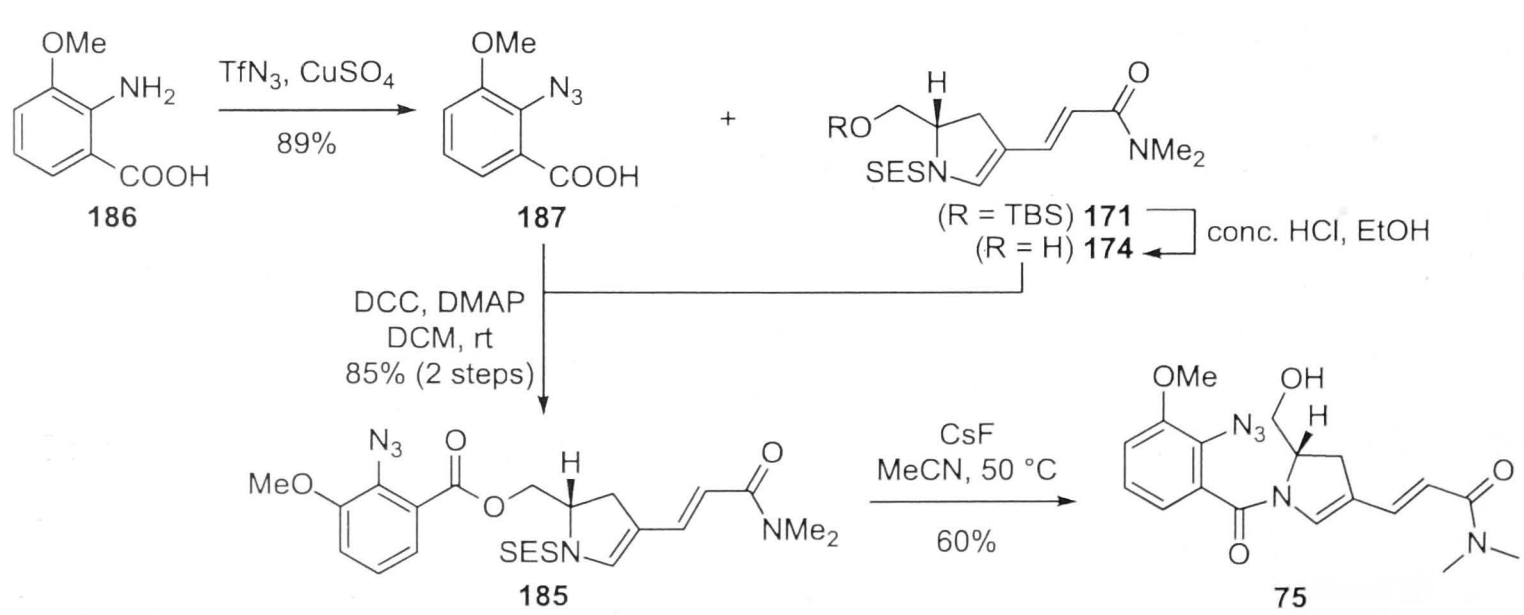


Scheme 4.15 *– Attempted SES deprotection in the presence of Boc anhydride*



Scheme 4.16 *– Proposed intramolecular substitution reaction*

Implementing this strategy required a coupling reaction between the primary alcohol **174** and the azido acid **187** which delivered the ester **185** in quantitative yield (Scheme 4.17). The azide **187** was synthesised from 2-amino-3-methoxybenzoic acid (**186**) following a procedure reported by Cavender and Shiner in excellent yield.[85] The conversion of the azide was confirmed by the presence of an absorbance band at 2114 cm^{-1}, which is indicative of the presence of an azide, in the IR spectrum. The ESI mass spectrum obtained for compound **185** displayed ions associated with the loss of a proton and nitrogen at *m/z* 192 and 164, respectively.



Scheme 4.17 *– Synthesis of benzoate* ***185*** *and subsequent deprotection*

The successful esterification was confirmed by the presence of an absorbance band at 2114 cm^{-1} in the IR spectrum. The ^1H NMR of compound **185** displayed a downfield shift

for the protons attached to C1′ from δ 3.79 ppm to δ 4.49 ppm which is consistent which the shift expected when converting a primary alcohol to an ester. The sodium adduct was also observed in the ESI mass spectrum obtained of the compound.

Fortunately, subjection of ester **185** to deprotection protocols employing a fluoride source did deliver the desired amide **75**.[64] The formation of this compound was confirmed by the disappearance of the resonances associated with the SES protecting group, at δ 3.09-3.03 (2H), 1.05-1.00 (2H), and 0.06 (9H) ppm, in the ^{1}H NMR as well as the expected upfield shift of the resonance corresponding to the protons attached to C1′ from δ 4.49 ppm to δ 3.91 ppm. The ESI mass spectrum obtained displayed an ion corresponding to the sodium adduct of this compound at m/z 394.

Optimisation of the intramolecular trapping of the SES deprotected molecule was undertaken in order to find a suitable fluoride source which can deliver reproducible results as well as improved yields. The fluoride sources investigated in this approach were TBAF, TASF and CsF. In small scale reactions, all three fluoride sources were observed to deliver the deprotected compound **75**. This result was confirmed by the observation of an ion corresponding to the sodium adduct at m/z 394 in the ESI mass spectrum in all cases. Although all three sources were successful in performing the desired transformation, CsF was chosen as the fluoride source with which to proceed as it could be more readily obtained and prepared in anhydrous form.[86]

Following the study on the fluoride sources, an investigation into the use of various solvents was also undertaken. Most reported deprotection protocols involving CsF have been performed in DMF due to the desirable solubility (0.60 mM at 24 °C) of the salt allowing for the presence of fluoride ions in solution.[76,78,80,81,87] Another advantage of the use of DMF is the 'naked anion' effect which allows for greater nucleophilicity of the fluoride ions as the solvent co-ordinates to the corresponding cation. Unfortunately, issues encountered during the removal of DMF from the final compound led to the trial of DMSO, THF and acetronitrile as alternate solvents.

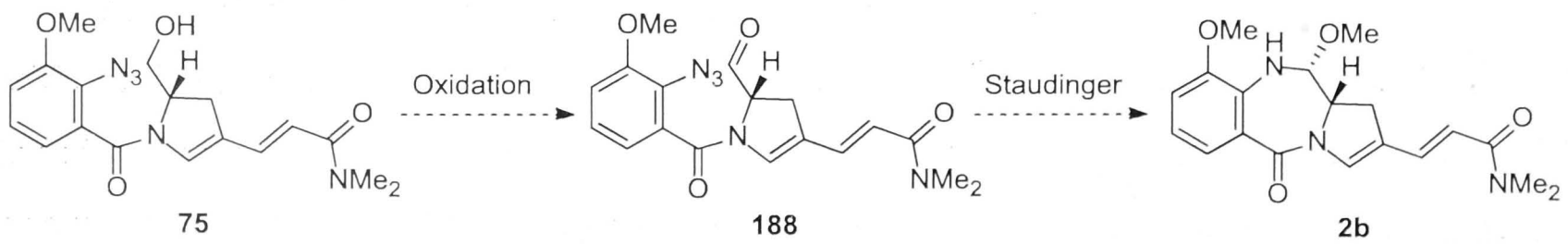
The use of DMSO in this reaction led to the observation of a faster reaction time while delivering less than 10% yield. It was postulated that the use of this solvent increased the 'naked anion' effect and thus a faster reaction time due to an increase in the nucleophilicity of the fluoride ions, when compared to DMF. However, the proposed increase in reactivity and difficulty in obtaining the solvent free from moisture led to degradation of the starting material and/or product and thus led to a lower yield. Due to the polar nature of compound **185**, the removal of this solvent from the small scale reaction also proved to be difficult leading to the need for extensive purification, which

could also lead to further degradation of material and account for the lower yield. As a result, further optimisation involving the use of this solvent was not undertaken.

While employing THF as the solvent for the reaction, the extremely limited solubility (0.093 mM at 24 °C) of CsF required 18-crown-6 (18c6) to be used as an additive to aid solvation (0.97 mM at 24 °C with 0.10 M of 18c6).[87] The use of 18c6 to co-ordinate and help solubilise CsF through co-ordination to the cesium cation would also create the naked anion effect, however the comparison of such an effect to solvents (DMSO > DMF > acetonitrile) in the absence of additives is not known. Unfortunately, after several attempts, it was found that 18-crown-6 was inherently difficult to remove from the final product and extensive purifications led to a decrease in yield. Thus, further optimisation involving this solvent was suspended while an effective solution for the removal of 18-crown-6 was sought.

Although CsF is known to have a comparatively lower solubility in acetonitrile (0.25 mM at 25 °C) as opposed to DMF,[87] it would still allow for a slow introduction of fluoride ions into the reaction mixture and allow the expected deprotection to take place. The use of acetonitrile would also result in a lower decreased 'naked anion' effect and thus lower the nucleophilicity and reactivity of the fluoride ions. The advantages of employing acetonitrile over DMF included the ability to obtain the solvent moisture-free and the lower boiling point of the solvent which allowed for easier removal of the solvent from the reaction mixture without extensive manipulations and extractions. The use of this solvent in the deprotection sequence allowed for a moderate 60% isolated yield of the diamide **75** (Scheme 4.17).

With the A- and C- rings assembled, attention was turned towards the completion of the synthesis by effecting an Staudinger reaction on the aldehyde **188** obtained from oxidation of the primary alcohol moiety in compound **75** (Scheme 4.18).



75 188 2b

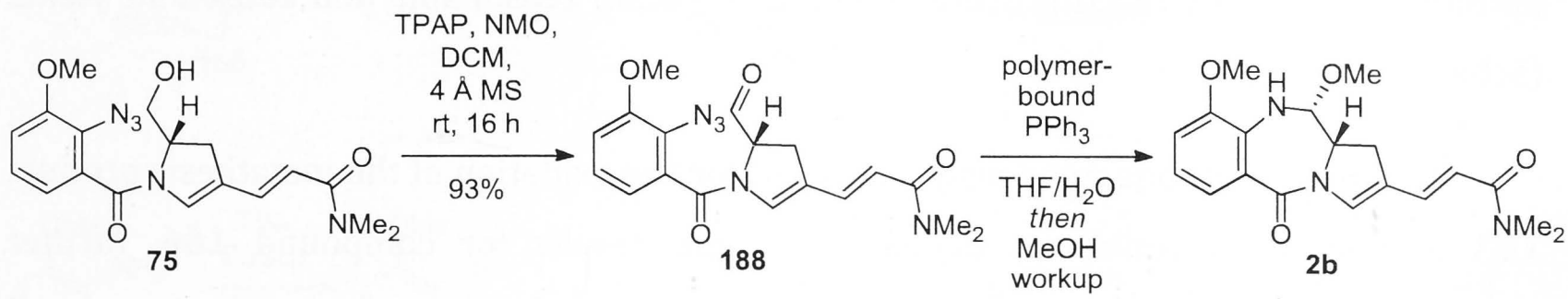
Scheme 4.18 *– Proposed oxidation and Staudinger reaction to form porothramycin B (**2b**)*

Several oxidation protocols were employed with varying results. The use of Dess-Martin's reagent allowed for the formation of the aldehyde **188**, however, due to the scale on which this reaction was performed (typically < 5 mg), the lack of consistent results and

the difficulty in removing all residual DMP by-products, even after a reductive work-up, led to the search for a protocol that would deliver a cleaner sample of the aldehyde **188**.

The Swern oxidation was also trialled, however, once again, due to the scale of the reaction (< 5 mg) and difficulty in removing residual DMSO from the reaction mixture, it was difficult to determine the presence of the aldehyde **188** in the crude reaction mixture and this approach was abandoned.

Finally, the Ley-Griffith oxidation employing tetrapropylammonium perutherate (TPAP) and *N*-methylmorpholine *N*-oxide (NMO) was attempted and this reaction was observed to deliver a cleaner sample of the aldehyde **188** in 93% yield (Scheme 4.19).[88] Whilst the yield is not an accurate indication of the success of the reaction as there were some impurities present, but the contaminats were determined to be only residual TPAP and NMO.



Scheme 4.19 *– Ley-Griffith oxidation of primary alcohol* ***75*** *and subsequent Staudinger reaction*

Having obtained several samples of the aldehyde **188**, albeit with varying purity, the Staudinger aza-Wittig reaction was attempted in the presence of polymer-bound triphenylphosphine in various solvents. The reaction was found to only proceed in THF/water and attempts to perform this reaction in DCM (to provide the product bearing a N10-C11 imine) or methanol [to provide porothramycin B (**2b**) directly] led to no reaction and eventual degradation of starting material over the course of the reaction. The product obtained, where THF/water was used as the solvent, would presumably be porothramycin A (**2a**) bearing a hemiaminal thus, in order to obtain the more stable porothramycin B (**2b**), work-up of the reaction involved several rounds of evaporation from a methanol solution to deliver the hemiaminal ether. The ^{1}H NMR obtained for this compound could not confirm the identity of the natural product due to the small amount of material obtained (< 1 mg) however, the ESI mass spectrum of the sample produced displayed ions corresponding to the proton adduct and sodium adduct of the target compound, at *m/z* 358 and 380 respectively.

4.2 Conclusion

The choice of the 2-trimethylsilylethanesulfonyl (SES) protecting group has allowed for the observation of traces of a compound bearing the same molecular weight as the target compound, porothramycin B (**2b**).

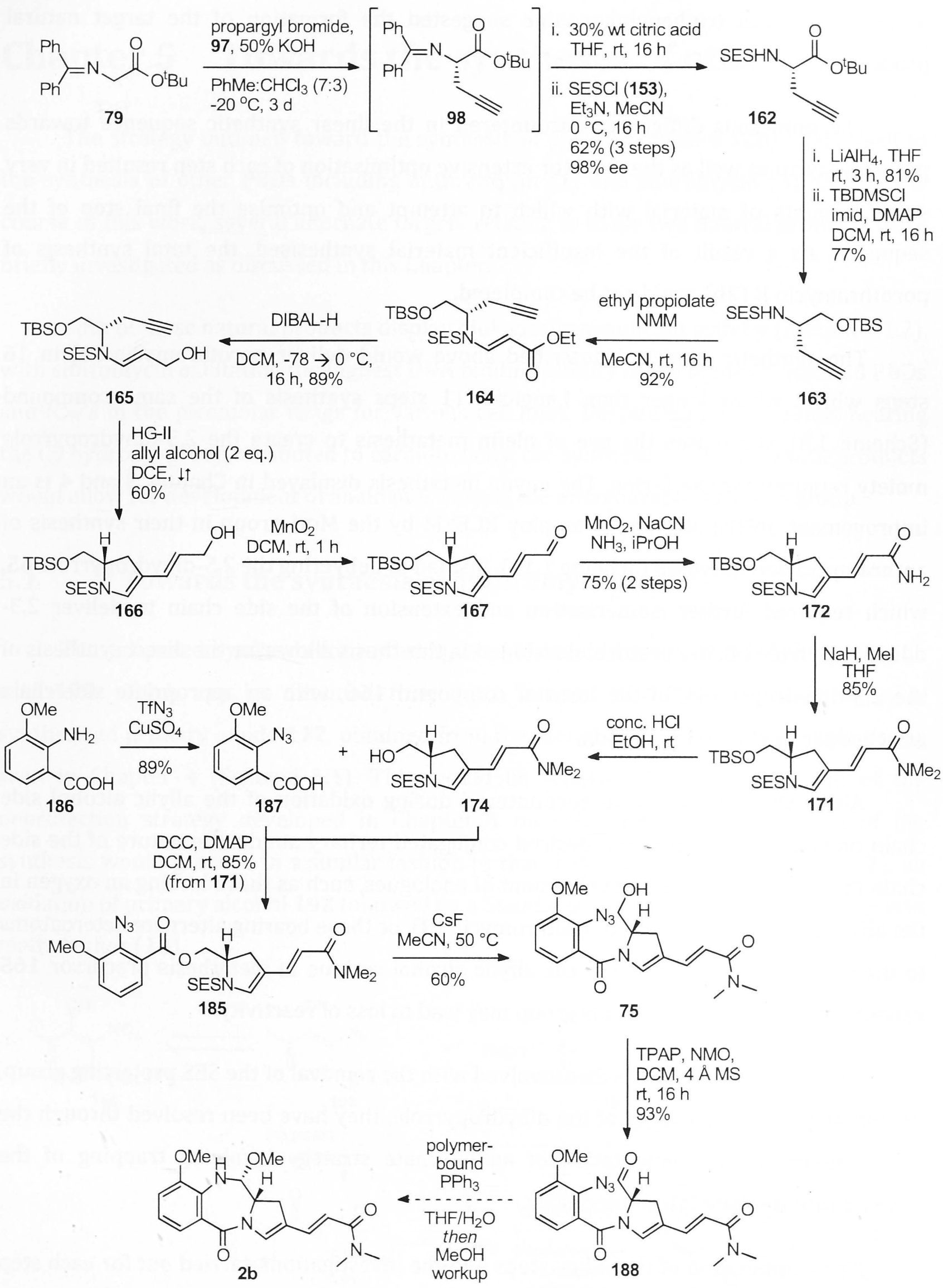
Access to the metathesis precursor **165** proceeded smoothly following the synthetic sequence developed through Chapters 2 and 3. Asymmetric alkylation of glycine imine **79** followed by several functional group interconversions yielded protected amino alcohol **163** which participated readily in an aza-Michael addition reaction to deliver the desired precursor **165** in 32% yield over 7 steps (Scheme 4.20).

The success of the metathesis rearrangement, first seen in Chapter 3, was reproduced with the SES protected derivative **165**. However, extensive studies and optimisations of this reaction were required to obtain reasonable and consistent yields (Scheme 4.20).

While the methods previously employed for the oxidation of the metathesis product **143** in Chapter 3 could not deliver the same results for compound **166**, further investigations into the use of manganese dioxide as an oxidant were met with success and delivered primary amide **172** (Scheme 4.20). Methylation of the primary amide moiety proceeded readily to give the requisite tertiary amide for porothramycin (**2**) in the form of compound **171**. It was postulated that the difficulties encountered in the oxidation of allylic alcohol **166**, in comparison to the tosyl derivative **143**, were due to the differing electronic properties of the protecting groups, even though both are sulfonamides.

With the desired C-ring and sidechain in hand, in the form of compound **171**, the removal of the SES protecting proved unsuccessful using protocols commonly employed for SES deprotection. The failure observed in the deprotection reaction may be explained by the formation of a potentially reactive dihydropyrrole moiety or amide anion, the expected product of the deprotection reaction, performing unwanted side reactions and leading to degradation of material.

In order to circumvent the observed degradation of material, the substrate was redesigned, so that after SES deprotection of ester **185**, the amide anion so formed could readily participate in an intramolecular substitution reaction to deliver the diamide **75** (Scheme 4.20). Although the desired transformation proceeded as expected, extensive optimisation of the deprotection was still undertaken in order to determine the ideal fluoride source and solvent for the reaction.



Scheme 4.20 – *Synthetic sequence for attempted synthesis of porothramycin B (**2b**)*

With the limited material obtained after the deprotection studies, an investigation into the various methods available for oxidation of the primary alcohol moiety to aldehyde **188** was also undertaken and it was found that the Ley-Griffith oxidation allowed for access to cleaner samples of the desired compound. Subjection of the aldehyde **188** to the Staudinger aza-Wittig reaction whilst using THF and water as the solvent in the presence

of polymer-bound triphenylphosphine suggested the formation of the target natural product **2b**.

The numerous difficulties encountered in the linear synthetic sequence towards porothramycin as well as the need for extensive optimisation of each step resulted in very small amounts of material with which to attempt and optimise the final step of the sequence. As a result of the insufficient material synthesised, the total synthesis of porothramycin B (**2b**) could not be completed.

The synthetic sequence described above would deliver porothramycin (**2**) in 16 steps which, whilst longer than Langlois' 11 steps synthesis of the same compound (Scheme 1.8), showcases the use of olefin metathesis to create the 2,3-dihydropyrrole moiety required for the C-ring. The enyne metathesis displayed in Chapter 3 and 4 is an improvement on the attempt to employ RCEYM by the Mori group in their synthesis of anthramycin derivative **65** (Scheme 1.11). Instead of delivering the 2,5-dihydropyrrole **65**, which required further isomerisation and extension of the side chain to deliver 2,3-dihydryopyrrole **68**, the protocol developed in this thesis allows for the direct synthesis of the 2,3-dihydropyrrole, in the form of compound **166**, with an appropriate side-chain attached for further manipulation.

Although problems were encountered during oxidation of the allylic alcohol side chain on compound **166** to the desired conjugated tertiary amide, the nature of the side chain may allow for further development of analogues, such as those lacking an oxygen in the allylic position, as observed in sibiromycin (**3**), or those bearing alternate heteroatoms in the same position. The use of the allylic alcohol residue in metathesis precursor **165** cannot be avoided as altering this group may lead to loss of reactivity.[54]

While there were also issues involved with the removal of the SES protecting group, presumably due to reactivity of the dihydropyrrole, they have been resolved through the development and implementation of an alternate strategy involving trapping of the reactive intermediate intramolecularly.

The combination of these key steps and the investigations carried out for each step has allowed for the design of a synthesis incorporating newly developed chemistry which may be applied to other PBDs of the same class, such as anthramycin (**1**) and sibiromycin (**3**).

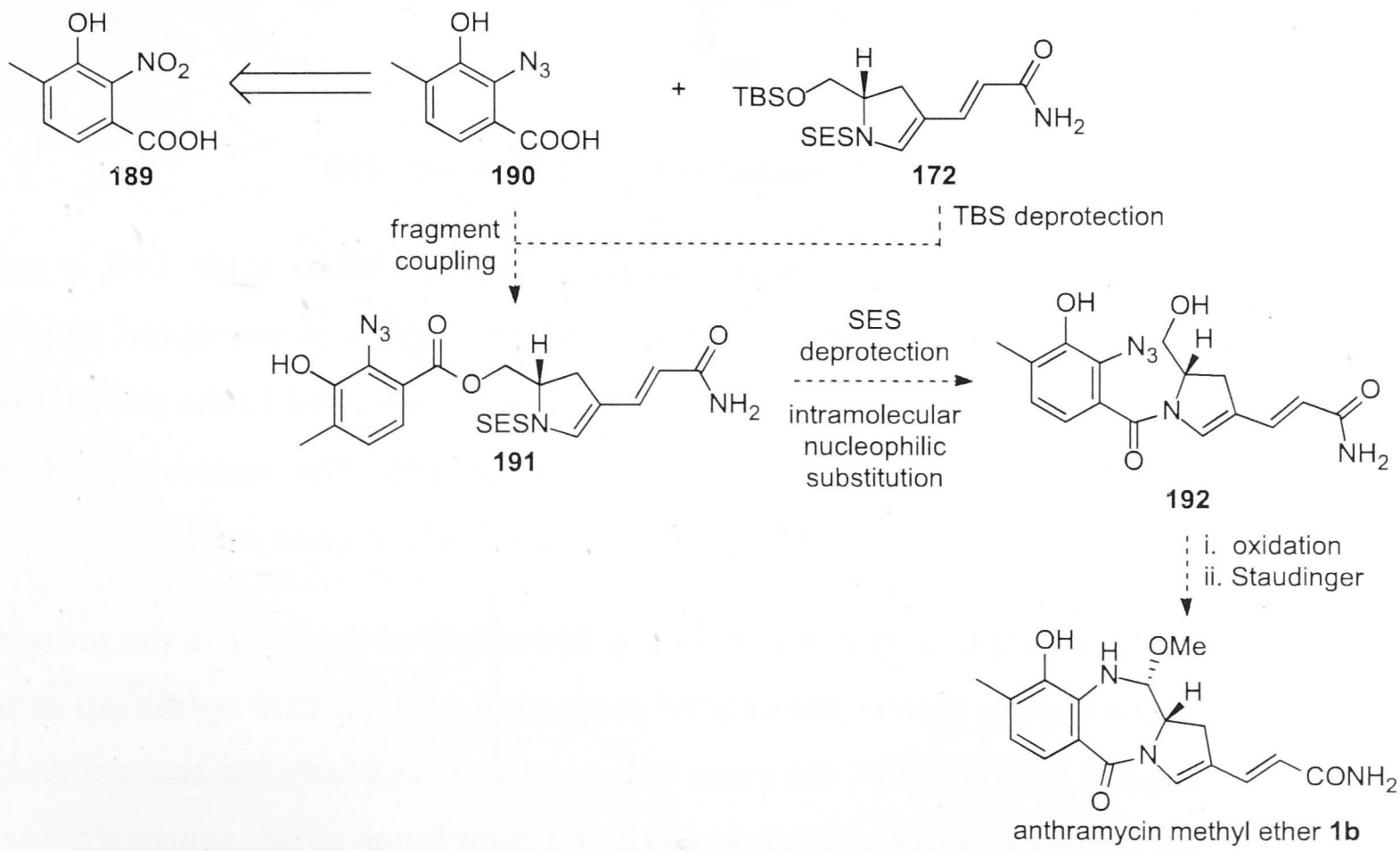
Chapter 5 Towards the syntheses of other PBDs

The strategy outlined toward the synthesis of porothramycin B (**2b**) lends itself to the synthesis of other PBDs including anthramycin (**1**) and sibiromycin (**3**). During the course of this work, several alternate targets relating to these two natural products were briefly investigated as discussed in this Chapter.

Both of these natural products display biologically significant activity (Section 1.1.2), with sibiromycin exhibiting the highest DNA binding affinity of the naturally isolated PBDs and IC_{50}'s in the picomolar range for various cell lines. Despite both compounds bearing the C9 hydroxyl group attributed to cardiotoxicity, the syntheses of these natural products would allow for development of analogues lacking the unfavourable hydroxyl group.

5.1 Towards the synthesis of anthramycin

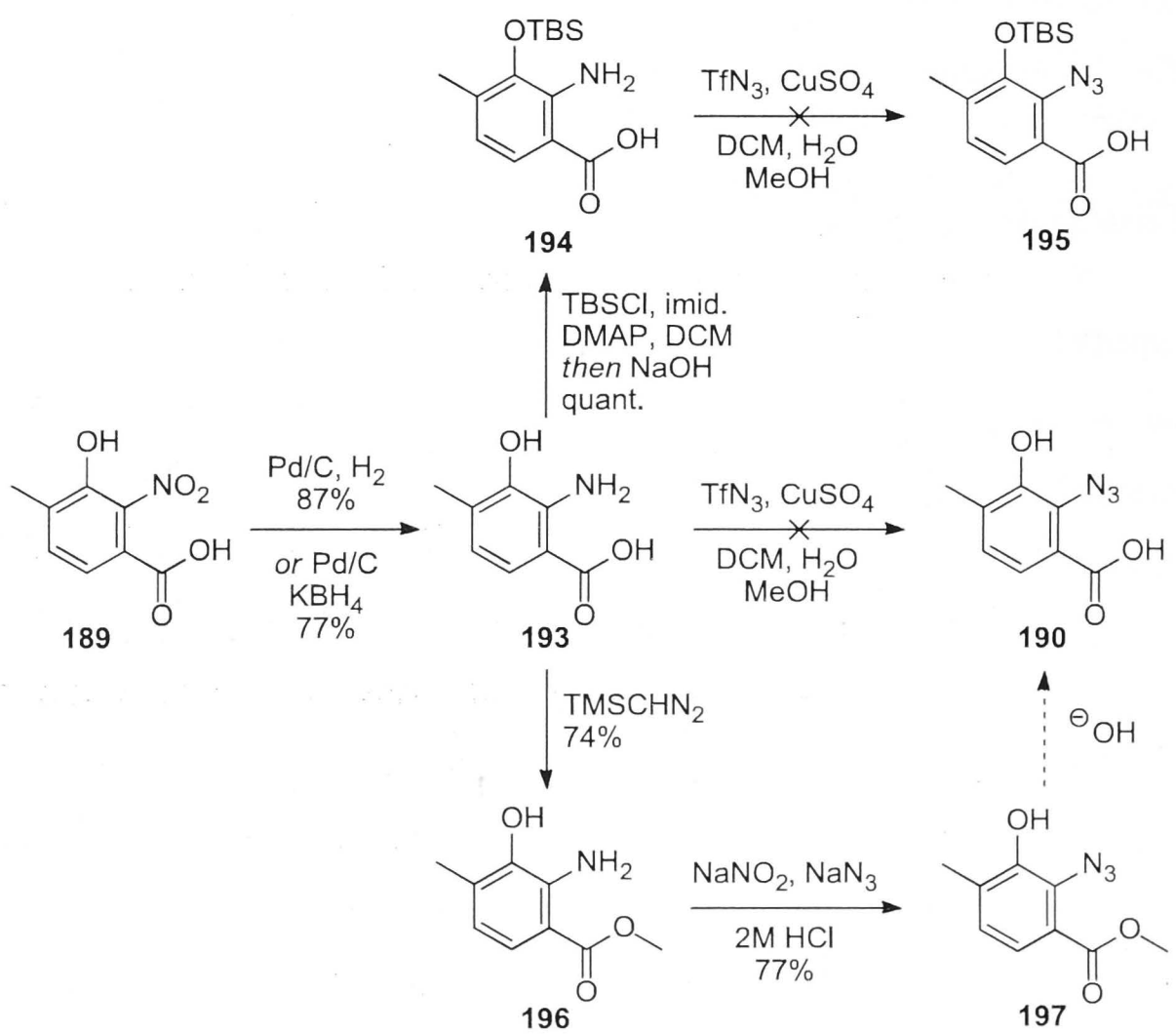
The proposed synthesis for anthramycin (**1**) would involve the coupling of azido acid **190**, which can be obtained from nitro benzoic acid **189**, to the previously synthesised primary amide **172**, obtained from the metathesis and oxidation sequence as seen in Chapter 4 (Scheme 5.1). This would be followed by implementation of the deprotection strategy developed in Chapter 4 on ester **191**. The completion of the synthesis would proceed in a similar fashion to that described for porothramycin (**2**), an oxidation of primary alcohol **192** followed by a Staudinger reaction to deliver anthramycin methyl ether (**1b**).



Scheme 5.1** – Proposed synthesis for anthramycin **(1b)

5.1.1 Attempts at synthesising azido acid for anthramycin

Several attempts were made towards to synthesis of azido acid **190** from 3-hydroxy-4-methyl-2-nitrobenzoic acid (**189**). Reduction of the nitro benzoic acid **189** to the corresponding anthranilic acid **193** proceeded smoothly and provided the desired compound in good yields (Scheme 5.2). Unfortunately, attempts to convert compound **193** to the azido derivative **190** were met with failure when employing the conditions described for the synthesis of azido acid **187**. The reactions performed consistently provided a red precipitate which may be attributed to the co-ordination of copper to the substrate. An attempt to perform this reaction with the phenol protected as the TBS ether **194** also failed and again led to the observation of a red precipitate.



Scheme 5.2 *– Attempted synthesis of azido acid* ***190***

Due to the unsuccessful attempts at converting amine **193** to azide **190**, a more traditional method, employing sodium nitrate and sodium azide, was attempted. In order to avoid any complications involving the acid moiety, it was converted to the methyl ester after reduction of the nitro moiety to give amino ester **196**. The conversion of this compound to the corresponding azide **197** proceeded smoothly in good yields.

Unfortunately, attempts to reveal the acid by hydrolysis of the ester in the presence of lithium hydroxide did not deliver the desired compound **190**. Further optimisation and investigation into the hydrolysis of the ester will need to be undertaken to provide the required acid derivative for coupling to amide **172** and completion of this synthesis.

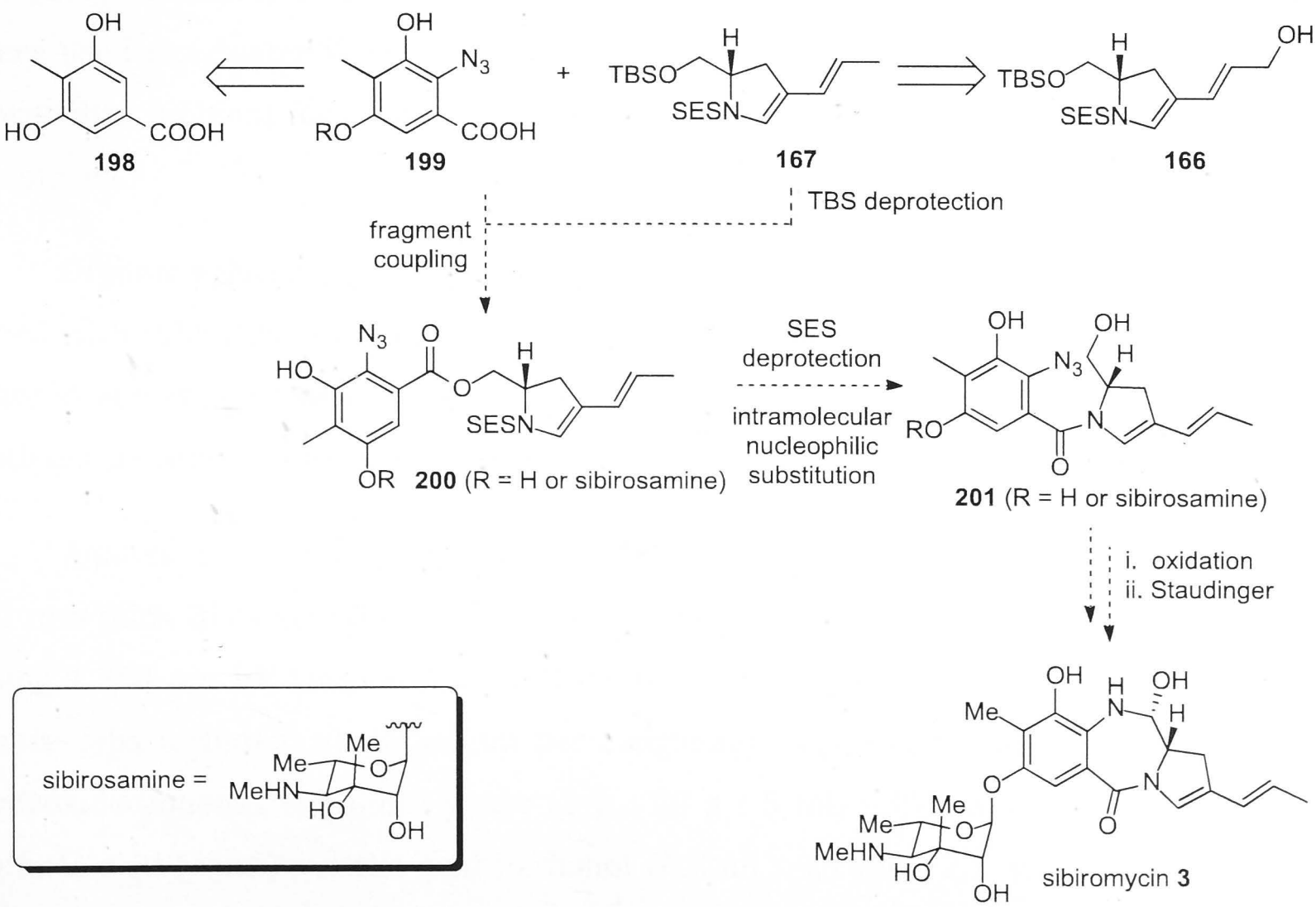
5.2 Proposed synthesis for sibiromycin

The proposed synthesis for sibiromycin (**3**) would involve the coupling of azido acid **199**, which may be synthesised from benzoic acid **198**, to the deoxygenated derivative **167** of the metathesis product **166** (Scheme 5.3).

The synthesis of compound **167** was briefly attempted during the investigation and optimisation of the metathesis reaction in Chapter 4 (Section 1.1.1, Scheme 4.4). Although the reaction did provide an insight into the metathesis rearrangement, the disappointing result in relation to the synthesis of compound **167** meant that an alternate route was required. The allylic oxygen may be removed by converting the alcohol to a good leaving group by the addition of a mesylate or sulfonate group followed by elimination by a hydride souce such as lithium aluminium hydride or Super Hydride®.[89,90]

The implementation of the deprotection strategy developed in Chapter 4 on ester **200** would deliver the diamide **201** and the completion of the synthesis would proceed in a similar fashion to that described for porothramycin (**2**), an oxidation of primary alcohol followed by a Staudinger reaction to deliver sibiromycin (**3**).

The synthesis and introduction of sibirosamine, which has been previously synthesised a number of times, is not discussed as this is beyond the scope of the strategy.[91-95]



Scheme 5.3 *- Proposed synthesis of sibiromycin* ***(3)***

Chapter 6 Experimental

6.1 General Experimental

Starting materials and reagents were obtained from the Sigma-Aldrich, Merck, TCI or Lancaster Chemical Companies and used as supplied or, occasionally, recrystallised or distilled. Inorganic salts were purchased from the Sigma-Aldrich, Alfa Aesar, AJAX, BDH or Unilab Chemical Companies.

THF, DMF, dichloromethane, acetonitrile and toluene were dried using a Glass Contour™ solvent purification system that is based upon a technology originally described by Grubbs et al.[96] Solvents were collected from the purification system as required.

Glassware was rinsed with acetone, dried then soaked in a base bath (Pyroneg® in water) before being rinsed with distilled water and oven-dried at 120 °C. Assembled apparatus was evacuated (<0.1 mm Hg) and flushed three times with dry nitrogen prior to use. Reaction mixtures were manipulated under nitrogen using standard Schlenk techniques.

Ambient temperature was assumed to be ca. 18 °C. Temperatures higher than ambient were attained using oil baths heated on a thermostated hot-plate stirrer. To attain temperatures lower than ambient for short periods of time, appropriate cooling baths were used (ice/water slurry, 0 °C; dry ice/acetone, −78 °C). To maintain temperatures lower than ambient for long periods of time, the Operon immersion cooler, IMC-90, was employed.

Organic solutions (extracts) obtained from the work-up of reaction mixtures were dried with anhydrous sodium sulfate (Na_2SO_4) or magnesium sulfate ($MgSO_4$) before being filtered and concentrated under reduced pressure on a rotary evaporator with a water bath temperature generally not exceeding 40 °C.

Analytical thin layer chromatography (TLC) was performed on aluminium-backed 0.2 mm thick silica gel 60 F_{254} plates as supplied by Merck. Eluted plates were visualised using a 254 nm UV lamp and/or by treatment with a suitable dip followed by heating. These dips included: a) potassium permanganate : potassium carbonate : 5% sodium hydroxide aqueous solution : water (3 g : 20 g : 5 mL : 300 mL); b) *p*-anisaldehyde : sulfuric acid (conc.) : acetic acid : ethanol (0.7 ml : 9.5 mL : 2.7 mL : 200 mL); and c) ninhydrin : acetic acid : ethanol (0.3 g : 3 mL : 100 mL)

Melting points were measured on a Stanford Research Systems Optimelt – Automated Melting Point System and are uncorrected.

Unless specified otherwise, proton (^1H) and carbon (^{13}C) NMR spectra were recorded at 20 °C on either a Varian Mercury 300 spectrometer (operating at 300 MHz for proton and 75 MHz for carbon nuclei) or a Varian MR400 spectrometer (operating at 400 MHz for proton and 100 MHz carbon nuclei) using $CDCl_3$ stored over K_2CO_3. For ^1H NMR, signals arising from the residual protio-forms of the solvent were used as the internal standard.[97] Chemical shifts are recorded as δ values in parts per million (ppm). ^1H NMR data are recorded as follows: chemical shift (δ) [multiplicity, coupling constant(s) J (Hz), relative integral] where multiplicity is defined as: s = singlet; d = doublet; t = triplet; q = quartet; m = multiplet or combinations of the above. For ^{13}C NMR spectra, the chemical shifts are referenced against with the central peak (δ 77.16) of the $CDCl_3$ "triplet". ^{13}C NMR data are recorded as follows: chemical shift (δ).

Infrared spectra (ν max) were recorded on a Perkin-Elmer 1800 Series FTIR Spectrometer. Samples were analysed as KBr discs (for solids) or as thin films on KBr plates (for liquids/oils).

Mass spectrometry was performed by the Australian National University's Mass Spectrometric Services Unit located in the Research School of Chemistry, Canberra, Australia. Low and high resolution electrospray (ES) mass spectra were recorded on a Micromass-Waters LC-ZMD single quadrupole liquid chromatograph-MS or a VG Quattro II triple quadrupole MS instrument operating in positive or negative ionisation mode. High performance liquid chromatography (HPLC) was performed on a Waters system consisting of a 600E quaternary pump and 2996 diode detector system.

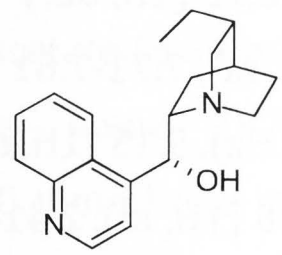
Optical rotations were measured between 17 to 20 °C on a Perkin-Elmer 241 polarimeter at the sodium-D line (λ = 589 nm) and the concentrations (c) (g/100 mL) indicated using spectroscopic grade chloroform ($CHCl_3$) as solvent. The measurements were carried out in a cell with a path length (l) of 1 dm. Specific rotations $[\alpha]_D$ were calculated using the equation $[\alpha]_D = (100\times\alpha)/(c\times l)$ and are given in $deg.dm^{-1}.cm^3.g^{-1}$.

Flash chromatography was performed using analytical grade solvents and silica gel 60 (230 – 400 mesh, 0.040 – 0.0063 mm) as supplied by Merck.[98]

Enantiomeric excess (*e.e.*) for compounds obtained after asymmetric alkylation were obtained by chiral HPLC analysis of the Boc derivative **155** on a Chiralcel OD-H (250 × 4.6 mm) column with 1% IPA in hexane (0.5 mL/min) as eluent (minor @ 12.9 min, major @ 14.1 min) with detection at 210 nm.

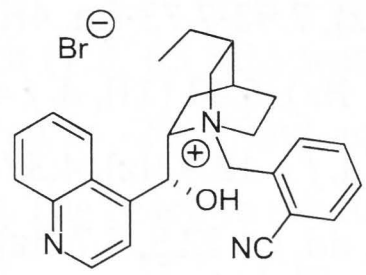
6.2 Experimental procedures for chapter 2

(–)-Hydrocinchonidine (103)[99]



Following a procedure reported by Lee and co-workers, a solution of (–)-cinchonidine (3.26 g, 11.1 mmol) in methanol (100 mL) was added 10% Pd-C (652 mg, 20% *w/w*) at rt. The reaction mixture was stirred under a hydrogen atmosphere for 20 h at this temperature then filtered through a pad of Celite™ and washed with methanol (2 × 50 mL). The filtrate was concentrated under reduced pressure then suspended in hexane (200 mL) and stirred for 1 h at rt. The solids were collected and dried under reduced pressure to afford **103** (2.48 g, 76%) as a white solid. m.p. 224-237 °C (lit.[100] m.p. 236-237 °C); $[\boldsymbol{\alpha}]_{\mathbf{D}}^{\mathbf{20}}$ -87.1 (*c* 0.396, CH_3OH) [lit.[100] $[\boldsymbol{\alpha}]_{\mathbf{D}}^{\mathbf{20}}$ -100.0 (*c* 0.386, CH_3OH)]; **IR** (film) 3068 (OH), 2943, 2924, 2866 (C-H), 1750, 1733, 1589, 1567, 1507 (C=C); **^{1}H NMR** (400 MHz, $CDCl_3$) δ 8.87 (1H, d, *J* = 4.4 Hz), 8.12 (1H, d, *J* = 8.4 Hz), 8.03 (1H, d, *J* = 8.4 Hz), 7.69 (1H, t, *J* = 7.6 Hz), 7.58 (1H, d, *J* = 4.4 Hz), 7.50 (1H, t, *J* = 7.2 Hz), 5.64 (1H, d, *J* = 4.4 Hz), 3.38 (1H, m), 3.14 (1H, m), 3.05 (1H, dd, *J* = 13.2, 10.0 Hz), 2.62 (1H, m), 2.38 (1H, m), 1.86-1.62 (3H, m), 1.52 (1H, m), 1.42 (2H, m), 1.25 (2H, m), 0.81 (3H, t, *J* = 7.2 Hz); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 150.4, 148.4, 130.5, 129.2, 126.8, 125.9, 123.2, 118.3, 72.4, 60.3, 58.8, 43.4, 37.7, 28.5, 27.8, 25.7, 21.8, 12.2; **MS** (ESI+) *m/z* 297 ($[M + H]^+$, 100%).

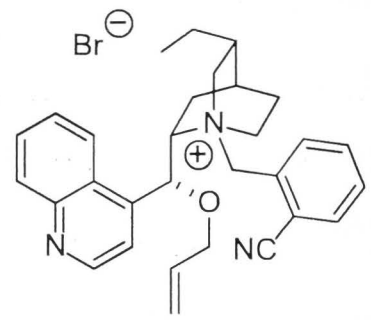
N-(2'-Cyanobenzyl)hydrocinchonidium bromide (104)[46]



A mixture of compound **103** (5.05 g, 17.0 mmol) and 2-cyanobenzyl bromide (3.67 g, 18.7 mmol) in a mixture of ethanol (12.5 mL), DMF (15 mL) and chloroform (5 mL) was stirred at 100 °C for 4 h. Upon cooling to room temperature, the reaction mixture was diluted with methanol (60 mL) and then added dropwise to diethyl ether (600 mL) with stirring. The solid precipitate was filtered and washed with diethyl ether (600 mL). The crude solid was then recrystallised from methanol/ether to afford target compound **104**

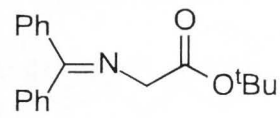
(5.71 g, 68%) as a light pink solid. m.p. 166 °C (lit.[46] m.p. 151 °C); $[\alpha]_D^{20}$ -132 (*c* 0.310, CH_3OH) [lit.[46] $[\alpha]_D^{25}$ -140 (*c* 0.555, CH_3OH)]; **IR** (film) 3128 (OH), 2958, 2824 (C-H), 2226 (C≡N), 1701, 1616, 1591, 1570, 1531, 1508 (C=C); **^{1}H NMR** (300 MHz, $CDCl_3$) δ 8.95 (1H, d, *J* = 4.5 Hz), 8.61 (1H, d, *J* = 7.8 Hz), 8.12 (1H, dd, *J* = 8.1, 1.4 Hz), 8.05 (1H, d, *J* = 8.1 Hz), 7.90 (1H, d, *J* = 4.5 Hz), 7.84-7.76 (2H, m), 7.71-7.61 (3H, m), 6.84 (1H, d, *J* = 5.4 Hz), 6.61 (1H, d, *J* = 12.3 Hz), 6.48 (1H, d, *J* = 6.3 Hz), 5.15 (1H, m), 4.92 (1H, d, *J* = 8.1 Hz), 3.86 (1H, t, *J* = 9.0 Hz), 3.24 (2H, d, *J* = 7.8 Hz), 3.08 (1H, m), 2.41-2.16 (2H, m), 2.02 (1H, d, *J* = 3.0 Hz), 1.83-1.67 (2H, m), 1.45-1.18 (3H, m), 0.77 (3H, t, *J* = 7.5 Hz); **MS** (ESI+) *m/z* 412 ([M - Br]$^+$, 100%).

_N_-(2'-Cyanobenzyl)- 9-(_O_-allyl)hydrocinchonidium bromide (97)[46]



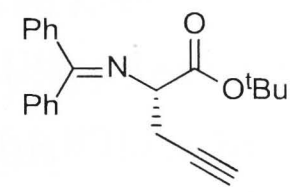
A suspension of **104** (5.53 g, 11.2 mmol) in dichloromethane (3.5 mL) was added allyl bromide (2.77 mL, 33.7 mmol) and 50% aqueous KOH (5.53 mL, 55.8 mmol) and stirred vigorously for 4 h at rt. The mixture was then diluted with water (10 mL) and extracted with dichloromethane (3 × 30 mL). The combined organic extracts were dried over $MgSO_4$, filtered and concentrated under reduced pressure. The resulting crude solid was recrystallised from dicholormethane/hexane to afford **97** (5.09 g, 85%) as an orange solid. m.p. 157 °C (lit. m.p. 165 °C); $[\alpha]_D^{20}$ -124 (*c* 0.666, CH_3OH) [lit.[46] $[\alpha]_D^{20}$ -154 (*c* 0.54, CH_3OH)]; **IR** (film) 3392 (Ar ring), 2957, 2875 (C-H), 2223, (C≡N), 1647, 1589, 1570, 1508 (C=C); **^{1}H NMR** (300 MHz, DMSO-d_6) δ 9.02 (1H, d, *J* = 4.5 Hz), 8.34 (1H, d, *J* = 8.4 Hz), 8.21-8.06 (2H, m), 7.97 (1H, d, *J* = 7.8 Hz), 7.92-7.73 (m, 4H), 7.70 (1H, d, *J* = 4.5 Hz), 6.51 (1H, s), 6.13 (1H, ddd, *J* = 22.8, 10.8, 5.4 Hz), 5.42 (1H, d, *J* = 17.4 Hz), 5.34 (1H, d, *J* = 12.9 Hz), 5.26 (1H, d, *J* = 10.5 Hz), 5.15 (1H, d, *J* = 12.9 Hz), 4.37 (1H, dd, *J* = 11.7, 5.1 Hz), 4.23 (1H, m), 4.11 (1H, t *J* = 9.0Hz), 3.97 (1H, dd, *J* = 12.3, 5.7 Hz), 3.66 (1H, d, *J* = 10.8 Hz), 3.44 (1H, d, *J* = 11.1 Hz), 3.32-3.21 (2H, m), 2.25 (1H, m), 2.13-2.02 (1H, m), 1.84-1.68 (2H, m), 1.53-1.36 (1H, m), 1.18-1.12 (2H, m), 0.70 (3H, t, *J* = 7.2 Hz); **^{13}C NMR** (100 MHz, DMSO-d_6) δ 150.1, 147.9, 140.8, 135.7, 134.2, 133.7, 133.6, 131.1, 130.5, 129.8, 129.5, 127.2, 125.0, 123.6, 119.6, 117.8, 117.7, 115.6, 69.3, 67.7, 61.6, 61.0, 51.2, 35.0, 30.8, 25.3, 24.9, 23.4, 20.7, 11.1; **MS** (ESI+) *m/z* 452 ([M - Br]$^+$, 100%).

tert-Butyl _N_-(diphenylmethyl-10-ene)glycinate (79)[101]



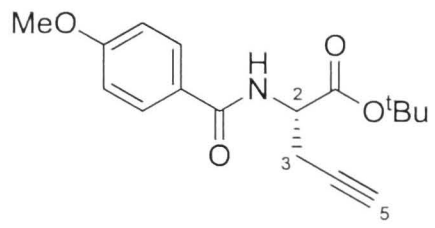
A solution of *tert*-butyl bromoacetate (8.56 mL, 58.0 mmol) in acetonitrile (60 mL) was treated with benzophenone imine (8.72 mL, 52.1 mmol) and *N,N*-diisopropylethylamine (10.1 mL, 58.0 mmol) and stirred at 70 °C for 14 h. The reaction mixture was allowed to cool to room temperature and concentrated under reduced pressure. The residue was partitioned between water (50 mL) and dichloromethane (50 mL), and the aqueous layer was extracted with dichloromethane (2 × 50 mL). The combined organic layers were dried over $MgSO_4$, filtered then concentrated. The crude mixture was crystallised using ethanol and collected. The filtrate was concentrated and crystallised from ethanol/petroleum ether in another two cycles to give a total yield of 11.9 g (77%) of imine **79** as a white powder. m.p. 111-112 °C (lit.[41] m.p. 111-115 °C); $\mathbf{R_f}$ 0.27 (10% ethyl acetate in hexane);[41] **IR** (film) 1740 (C=O); **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.67-7.65 (2H, m, phenyl-H), 7.48-7.30 (6H, m, phenyl-H), 7.20-7.17 (2H, m, phenyl-H), 4.12 (2H, s, CH_2), 1.46 (9H, s, $C(CH_3)_3$); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 171.6, 169.9, 139.5, 136.3, 130.5, 128.9, 128.9, 128.7, 128.2, 127.8, 81.2, 56.5, 28.2; **MS** (ESI+) *m/z* 296 ($[M + H]^+$, 30%); 318 ($[M + Na]^+$, 60%).

(*S*)-*tert*-Butyl 2-(diphenylmethyl-10-ene)pent-4-ynoate (98)[46]



A solution of imine **79** (3.54 g, 11.98 mmol) and phase transfer catalyst **97** (0.638 g, 1.198 mmol) in toluene/chloroform (7:3, 63 mL) was added propargyl bromide (9 mL, 60.5 mmol). The mixture was cooled to -20 °C and aqueous potassium hydroxide (50% w/v, 4.5 mL, 40.1 mmol) was added. The reaction mixture was stirred at -20 °C for 2 d then warmed to room temperature and concentrated. The residue was partitioned between diethyl ether (75 mL) and water (75 mL) and the aqueous layer was extracted with dichloromethane (3 × 75 mL). The combined organic layers were dried with $MgSO_4$, filtered and concentrated under reduced pressure to afford imine **98** in a crude mixture as a light brown oil. The crude mixture was used in the next step without purification.

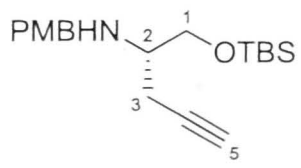
(*S*)-*tert*-Butyl 2-(4-methoxybenzamido)pent-4-ynoate (105)



A solution of imine **98** (20.0 mmol) in tetrahydrofuran (150 mL) was added aqueous citric acid (30% w/v, 46.1 mL, 60.0 mmol), and the mixture was stirred at rt for 20 h. The reaction mixture was then concentrated under reduced pressure, diluted with diethyl ether (100 mL) and extracted twice with hydrochloric acid (1*M*, 3 × 100 mL). The combined aqueous layers were basified to pH ~8-9 with solid sodium bicarbonate and extracted with ethyl acetate (3 × 100 mL). The combined organic layers were dried with $MgSO_4$, filtered and concentrated under reduced pressure to afford a light brown oil.

To a solution of the above oil in dichloromethane (100 mL) was added *p*-anisoyl chloride (4.1 mL, 30.3 mmol) and triethylamine (4.2 mL, 30.1 mmol) at rt and the reaction was stirred for 16 h. The reaction mixture was added water (50 mL) and separated. The aqueous layer was extracted with dichloromethane (3 × 75 mL). The combined organic layers were dried with $MgSO_4$, filtered and concentrated under reduced pressure to afford a light brown oil. The crude mixture was purified by flash chromatography (gradient elution of 5-10% ethyl acetate in hexane) to yield ester **105** (3.62 g, 59%, 95% *ee*) from imine **98** as a pale yellow oil. $[\alpha]_D^{20}$ +67.7 (*c* 1.80, $CHCl_3$); R_f 0.06 (10% ethyl acetate in hexane); **IR** (film) 3429 (N-H), 3297 (CC-H), 3003, 2978, 2935, 2840 (C-H), 2122 (C≡CH), 1731, 1644 (C=O), 1606, 1578, 1533, 1503 (C=C); **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.80 (2H, d, *J* = 8.4 Hz, Ar-H), 6.93 (3H, d, *J* = 8.4 Hz, Ar-H & NH), 4.79 (1H, m, H_2), 3.84 (3H, s, OMe), 2.86 (2H, m, H_3), 2.03 (1H, s, H_5) 1.51 (9H, s, $C(CH_3)_3$); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 169.8, 166.4, 162.5, 129.0, 126.3, 113.8, 83.0, 78.9, 71.4, 55.5, 51.4, 28.1, 22.9; **MS** (ESI+) *m/z* 304 ($[M + Na]^+$, 5%), 336 ($[M + Na]^+$, 100%), 342 ($[M + K]^+$, 30%); **HRMS** (ESI+) calcd for $C_{17}H_{21}NO_4Na$: 326.1368, found 326.1360, calcd for $C_{17}H_{21}NO_4K$: 342.1108, found 342.1103.

(*S*)-1-(*tert*-Butyldimethylsilyloxy)-*N*-(4-methoxybenzyl)pent-4-yn-2-ylamine (99)

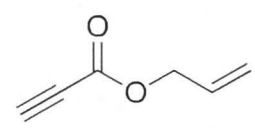


To a solution of ester **105** (3.62 g, 11.9 mmol) in diethyl ether (250 mL) was added lithium aluminium hydride (1.36 g, 35.8 mmol) at 0 °C and the reaction stirred at rt for 3 h. The reaction mixture was then cooled to 0 °C and diluted with diethyl ether (125 mL),

treated with water (1.5 mL), NaOH (3*M*, 1.5 mL) and water (5 mL), and added $MgSO_4$. The mixture was stirred for a further 15 min, then filtered through a pad of Celite™ and concentrated under reduced pressure to give a yellow oil. The crude alcohol was used in the next step without further purification. **^{1}H NMR** (300 MHz, $CDCl_3$) δ 7.27-7.23 (2H, m, Ar-H), 6.89-6.85 (2H, m, Ar-H), 3.84-3.68 (2H, m, Ar-CH_2), 3.80 (3H, s, OCH_3), 3.66 (1H, dd, J = 10.8, 4.2 Hz, H_{1a}), 3.46 (1H, dd, J = 10.8, 6.6 Hz, H_{1b}), 2.69 (1H, qd, J = 6.0, 4.5 Hz, H_2), 2.49-2.32 (2H, m, H_3), 2.17 (2H, bs, NH & OH), 2.03 (1H, t, J = 2.7 Hz, H_5); **^{13}C NMR** (75 MHz, $CDCl_3$) δ 158.8, 131.9, 129.4, 113.9, 80.8, 70.9, 62.9, 56.5, 55.3, 50.4, 20.9.

To a solution of the above alcohol (11.9 mmol) in dichloromethane (100 mL) was added *tert*-butyldimethylsilyl chloride (2.71 g, 18.0 mmol), imidazole (1.23 g, 18.0 mmol) and DMAP (73.3 mg, 0.6 mmol) and the reaction was stirred at rt for 16 h. The reaction mixture was added water (100 mL) and extracted with dichloromethane (2 × 100 mL). The combined organic layers were dried with $MgSO_4$, filtered and concentrated under reduced pressure. The crude mixture was purified by flash chromatography (gradient elution of 5-10% ethyl acetate in hexane) to yield silyl ether **99** (2.85 g, 72%) as a yellow oil. $[\alpha]_D^{20}$ +8.5 (*c* 1.65, $CHCl_3$); R_f 0.34 (10% ethyl acetate in hexane); **IR** (film) 3635 (N-H), 3309 (CC-H), 3030, 2998, 2929, 2856 (C-H), 2117 (C≡CH), 1612, 1585, 1512 (C=C); **^{1}H NMR** (300 MHz, $CDCl_3$) δ 7.26-7.23 (2H, m, Ar-H), 6.87-6.84 (2H, m, Ar-H), 3.84-3.69 (2H, m, Ar-CH_2), 3.78 (3H, s, OCH_3), 3.68-3.62 (2H, m, H_1), 2.86-2.80 (1H, m, H_2), 2.41-2.37 (2H, m, H_2),2.03 (1H, bs, NH), 1.98 (1H, t, J = 2.7 Hz, H_5), 0.89 (9H, s, $C(CH_3)_3$), 0.06 (6H, s, $SiCH_3$); **^{13}C NMR** (75 MHz, $CDCl_3$) δ 158.7, 132.4, 129.3, 113.8, 81.6, 70.1, 64.0, 57.1, 55.3, 50.7, 26.0, 20.8, 18.3, -5.3; **MS** (ESI+) *m/z* 334 ($[M + H]^+$, 100%); **HRMS** (ESI+) calcd for $C_{19}H_{32}NO_2Si$: 334.2202, found 334.2207.

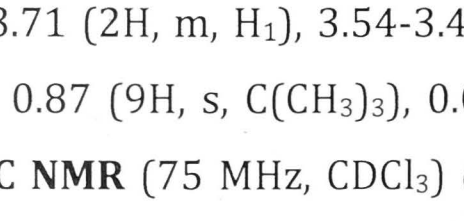
Allyl propiolate[102]



Following a procedure reported by Balas and Longwost,[102] a solution of propiolic acid (3.56 g, 50.8 mmol) and allyl alcohol (4.7 mL, 94.8 mmol) in THF (100 mL) was added a solution of DMAP (423 mg, 3.46 mmol) and DCC (10.62 g, 51.5 mmol) in THF (24 mL) at -20 °C. The reaction mixture was allowed to warm to room temperature and stirred at this temperature for 14 h. The reaction mixture was filtered and the filtrate was washed with aq. HCl (1M, 100 mL), and brine (100 mL). The organic layer was then dried with $MgSO_4$,

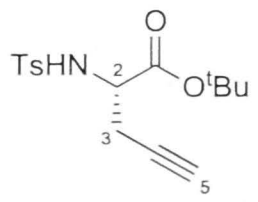
filtered and concentrated under reduced pressure. Distillation of the crude mixture furnished allyl propiolate as a clear, colourless oil (3.24 g, 61%). The spectroscopic data obtained for this compound correlated with those previously reported.[102]

(*S,E*)-Prop-1-en-3-yl 3-(*N*-(1-(*tert*-butyldimethylsilyloxy)pent-4-yn-2-yl)-*N*-(4-methoxybenzyl)amino)propenoate (100)



To a solution of silyl ether **99** (518 mg, 1.55 mmol) in acetonitrile (20 mL) was added allyl propiolate (200 mg, 1.82 mmol) and the reaction was allowed to stir at reflux for 16 h. The reaction mixture was cooled to rt and concentrated under reduced pressure. The crude mixture was purified by flash chromatography (10% ethyl acetate in hexane) to yield conjugated ester **100** (680 mg, 99%) as a pale yellow oil. $[\alpha]_D^{20}$ -25.0 (*c* 1.11, $CHCl_3$); R_f 0.17 (10% ethyl acetate in hexane); **IR** (film) 3293 (CC-H), 3083, 2953, 2930, 2857 (C-H), 2121 (C≡CH), 1690 (C=O), 1647, 1607, 1513 (C=C); **^{1}H NMR** (300 MHz, $CDCl_3$) δ 7.70 (1H, d, *J* = 13.2 Hz, $H_{2'}$), 7.18-7.15 (2H, m, Ar-H), 6.85-6.82 (2H, m, Ar-H), 5.94 (1H, ddt, *J* = 17.1, 10.2, 5.7 Hz, $H_{6'}$), 5.28 (1H, app. dq, *J* = 17.4, 1.5 Hz, $H_{7'}$), 5.28 (1H, app. dq, *J* = 10.5, 1.5 Hz, $H_{7'}$), 4.71 (1H, d, *J* = 13.2 Hz, $H_{1'}$), 4.56 (2H, dt, *J* = 5.7, 1.5 Hz, $H_{5'}$), 4.34 (2H, s, Ar-H), 3.79 (3H, s, OCH_3), 3.73-3.71 (2H, m, H_1), 3.54-3.46 (1H, m, H_2), 2.58-2.40 (2H, m, H_3), 2.03 (1H, t, *J* = 2.8 Hz, H_5), 0.87 (9H, s, $C(CH_3)_3$), 0.022 (3H, s, $SiCH_3$), 0.017 (3H, s, $SiCH_3$), 0.04 (9H, s, $Si(CH_3)_3$); **^{13}C NMR** (75 MHz, $CDCl_3$) δ 169.3, 159.0, 150.9(bs), 133.6, 128.4(bs), 117.3, 114.2, 86.2(bs), 80.4, 71.2, 64.0, 63.5(bs), 55.4, 52.1(bs), 25.9, 20.4(bs), 18.3, -5.4, -5.5 [signals marked with (bs) indicate that the signal was a broad singlet]; **MS** (ESI+) *m/z* 444 ($[M + H]^+$, 100%), 466 ($[M + Na]^+$, 70%); **HRMS** (ESI+) calcd for $C_{25}H_{38}NO_4Si$: 444.2570, found 444.2570, $C_{25}H_{37}NO_4SiNa$: 466.2390, found 466.2389.

(*S*)-*tert*-Butyl 2-(4-methylbenzenesulfonamido)pent-4-ynoate (117)

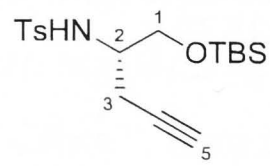


A solution of imine **98** (7.99 mmol) in tetrahydrofuran (70 mL) was added aqueous citric acid (30% w/v, 15.35 mL, 24.0 mmol), and the mixture was stirred at rt for 20 h. The

reaction mixture was then concentrated under reduced pressure, diluted with diethyl ether (50 mL) and extracted with hydrochloric acid (1*M*, 3 × 50 mL). The combined aqueous layers were basified to pH ~8-9 with solid sodium bicarbonate and extracted with ethyl acetate (3 × 70 mL). The combined organic layers were dried with $MgSO_4$, filtered and concentrated under reduced pressure to afford a light brown oil.

To a solution of the above oil in dichloromethane (25 mL) was added *p*-toluenesulfonyl chloride (1.68 g, 8.81 mmol) and triethylamine (3.40 mL, 24.2 mmol) at rt and the reaction was stirred for 16 h. The reaction mixture was added to water (25 mL) and was extracted with dichloromethane (2 × 50 mL). The combined organic layers were dried with $MgSO_4$, filtered and concentrated under reduced pressure to afford a light brown oil. The crude mixture was purified by flash chromatography (gradient elution of 5-10% ethyl acetate in hexane) to yield ester **117** (1.84 g, 71%, 95% *ee*) from imine **98** as a white solid (m.p. 75 °C); $[\alpha]_D^{20}$ +6.7 (*c* 1.00, $CHCl_3$); R_f 0.07 (10% ethyl acetate in hexane); **IR** (film) 3285 (CC-H), 2980, 2931 (C-H), 2123 (C≡CH), 1730 (C=O), 1598 (C=C); **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.74 (2H, d, *J* = 8.4 Hz, Ar-H), 7.29 (2H, d, *J* = 8.0 Hz, Ar-H), 5.39 (1H, d, *J* = 8.8 Hz, NH), 3.97 (1H, m, H_2), 2.65 (2H, m, H_3), 2.41 (3H, s, Ar-Me), 2.01 (1H, t, *J* = 2.8 Hz, H_5), 1.32 (9H, s, $C(CH_3)_3$); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 168.4, 143.6, 136.9, 129.6, 127.2, 83.1, 77.8, 72.1, 54.3, 27.6, 24.3, 21.4; **MS** (ESI+) *m/z* 362 ([M + K]$^+$, 100%), 346 ([M + Na]$^+$, 80%); **HRMS** (ESI+) calcd for $C_{16}H_{21}NO_4SNa$: 346.1089, found 346.1088, calcd for $C_{16}H_{21}NO_4SK$: 362.0828, found 362.0830.

(*S*)-*N*-(1-(*tert*-Butyldimethylsilyloxy)pent-4-yn-2-yl)-4-methylbenzenesulfonamide (118)

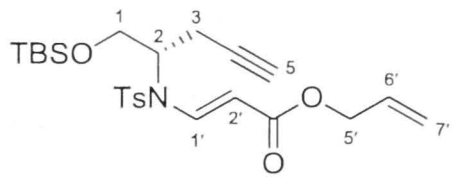


To a solution of ester **117** (1.84 g, 5.69 mmol) in tetrahydrofuran (100 mL) was added lithium aluminium hydride (0.646 g, 17.0 mmol) at 0 °C and the reaction stirred at rt for 1 h. The reaction mixture was then cooled to 0 °C and diluted with diethyl ether (125 mL), treated with water (0.6 mL), NaOH (3*M*, 0.6 mL) and water (1.8 mL), and dried with $MgSO_4$. The mixture was then stirred for a further 15 min and filtered through a pad of Celite™, then concentrated under reduced pressure. The crude mixture was purified by flash chromatography (30% ethyl acetate in hexane) to yield the corresponding alcohol (1.25 g, 87%) as a clear, colourless oil. $[\alpha]_D^{20}$ -51.8 (*c* 1.30, $CHCl_3$); R_f 0.12 (30% ethyl acetate in hexane); **IR** (film) 3485 (O-H), 3287 (CC-H), 2961, 2921, 2883 (C-H), 2120

(C≡CH), 1597 (C=C); **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.77 (2H, d, *J* = 8.0 Hz, Ar-H), 7.29 (2H, d, *J* = 8.4 Hz, Ar-H), 5.46 (1H, d, *J* = 8.4 Hz, NH), 3.65 (2H, m, H_1), 3.40 (1H, m, H_2), 2.63 (1H, m, OH), 2.41 (3H, s, Ar-Me), 2.26 (2H, m, H_3), 1.95 (1H, t, *J* = 2.8 Hz, H_5); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 143.8, 137.4, 129.9, 127.2, 79.5, 71.6, 63.4, 53.5, 21.6; **MS** (ESI+) *m/z* 254 ($[M + H]^+$, 10%), 276 ($[M + Na]^+$, 45%), 292 ($[M + K]^+$, 35%); **HRMS** (ESI+) calcd for $C_{12}H_{16}NO_3S$: 254.0851, found 254.0851, calcd for $C_{12}H_{15}NO_3SNa$: 276.0670, found 276.0670, calcd for $C_{12}H_{15}NO_3SK$: 292.0410, found 292.0410.

To a solution of the above alcohol (1.25 g, 4.93 mmol) in dichloromethane (100 mL) was added *tert*-butyldimethylsilyl chloride (1.12 g, 7.43 mmol), imidazole (0.505 g, 7.41 mmol) and DMAP (30 mg, 0.246 mmol) and the reaction was stirred at rt for 16 h. The reaction mixture was added water (50 mL) and extracted with dichloromethane (2 × 50 mL). The combined organic layers were dried with $MgSO_4$, filtered and concentrated under reduced pressure. The crude mixture was purified by flash chromatography (gradient elution of 5-10% ethyl acetate in hexane) to yield silyl ether **118** (1.61 g, 89%) as a clear, colourless oil. $[\alpha]_D^{20}$ -4.9 (*c* 0.448, $CHCl_3$); R_f 0.16 (10% ethyl acetate in hexane); **IR** (film) 3291 (CC-H), 3065, 2954, 2929, 2884, 2857 (C-H), 2121 (C≡CH), 1644, 1599 (C=C); **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.76 (2H, d, *J* = 8.4 Hz, Ar-H), 7.30 (2H, d, *J* = 8.0 Hz, Ar-H), 4.92 (1H, d, *J* = 8.4 Hz, NH), 3.66 (1H, dd, *J* = 10.0, 3.6 Hz, H_{1a}), 3.45 (1H, dd, *J* = 10.0, 5.2 Hz, H_{1b}), 3.42-3.34 (1H, m, H_2), 2.47 (1H, ddd, *J* = 16.8, 4.4, 2.8 Hz, H_{3a}), 2.42 (3H, s, OCH_3), 2.31 (1H, ddd, *J* = 16.8, 8.0, 2.8 Hz, H_{3b}), 1.93 (1H, t, *J* = 2.8 Hz, H_5), 0.84 (9H, s, $C(CH_3)_3$), 0.00 (3H, s, $SiCH_3$), -0.01 (3H, s, $SiCH_3$); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 143.6, 137.8, 129.9, 127.2, 79.8, 71.1, 62.9, 53.3, 25.9, 21.6, 18.3, -5.4 (2C); **MS** (ESI+) *m/z* 368 ($[M + H]^+$, 20%), 390 ($[M + Na]^+$, 100%); **HRMS** (ESI+) calcd for $C_{18}H_{30}NO_3SSi$: 368.1718, found 368.1725, calcd for $C_{18}H_{29}NO_3SSiNa$: 390.1535, found 390.1529.

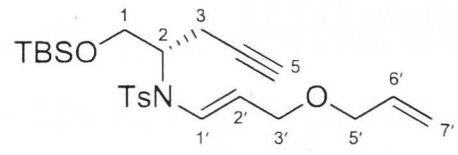
(*S,E*)-Prop-1-en-3-yl 3-(*N*-(1-(*tert*-butyldimethylsilyloxy)pent-4-yn-2-yl)-4-methylbenzenesulfonamido)propenoate (119)



To a solution of silyl ether **118** (99.9 mg, 0.27 mmol) in acetonitrile (2 mL) was added allyl propiolate (38.9 mg, 0.35 mmol) and *N*-methylmorpholine (35.7 mg, 0.35 mmol) and the reaction was allowed to stir at rt for 16 h. The reaction mixture was then

concentrated under reduced pressure and the crude residue was purified by flash chromatography (5-10% ethyl acetate in hexane) to yield conjugated ester **119** (128.6 g, 99%) as a pale yellow oil. $[\alpha]_D^{20}$ +15.8 (*c* 0.46, $CHCl_3$); R_f 0.49 (30% ethyl acetate in hexane); **IR** (film) 3293 (CC-H), 3067, 2953, 2929, 2884, 2857 (C-H), 2123 (C≡C), 1713 (C=O), 1624, 1598 (C=C); **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.76 (2H, d, *J* = 8.1 Hz, Ar-H), 7.70 (2H, d, *J* = 14.4 Hz, $H_{2'}$), 7.29 (1H, d, *J* = 8.1 Hz, Ar-H), 5.96-5.83 (1H, m, $H_{6'}$), 5.67 (1H, d, *J* = 14.4 Hz, $H_{1'}$), 5.27 (1H, d, *J* = 17.1 Hz, $H_{7'a}$), 5.18 (1H, d, *J* = 10.5 Hz, $H_{7'b}$), 4.58 (2H, d, *J* = 5.7 Hz, $H_{5'}$), 4.45-4.36 (1H, m, H_2), 3.88-3.78(1H, m, H_1), 3.19 (2H, m, CH_2SO_2), 2.67 (1H, ddd, *J* = 17.1, 7.5, 2.4 Hz, H_{3a}), 2.50 (1H, ddd, *J* = 17.1, 7.5, 2.4 Hz, H_{3b}), 2.40 (3H, s, Ar-CH_3), 1.85 (1H, t, *J* = 2.8 Hz, H_5), 0.82 (9H, s, $C(CH_3)_3$), -0.007 (3H, s, $SiCH_3$), -0.012 (3H, s, $SiCH_3$); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 166.9, 144.9, 140.4, 135.6, 132.6, 129.9, 129.7, 117.9, 100.5, 79.4, 71.3, 64.8, 63.0, 59.7, 25.8, 21.6, 19.5, 18.2, -5.56, -5.62; **MS** (ESI+) *m/z* 500 ($[M + Na]^+$, 100%), 478 ($[M + H]^+$, 12%); **HRMS** (ESI+) calcd for $C_{24}H_{36}NO_5SSi$: 478.2083, found 478.2086, $C_{24}H_{35}NO_5SSiNa$: 500.1903, found 500.1903.

(*S,E*)-*N*-(3-(Prop-1-en-3-yloxy)prop-1-enyl)-*N*-(1-(*tert*-butyldimethylsilyloxy)pent-4-yn-2-yl)-4-methylbenzenesulfonamide (122)



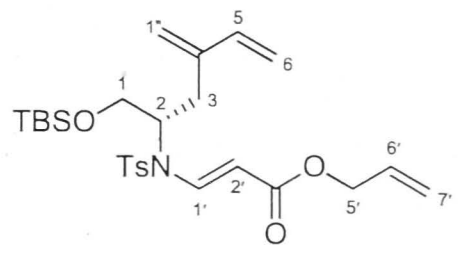
To a solution of conjugated ester **119** (39.6 mg, 0.08 mmol) in dichloromethane (0.5 mL) was added a solution of diisobutylaluminium hydride in hexanes (1.0*M*, 249 μL, 0.25 mmol) at -78 °C and allowed to stir at this temperature for 2 h. The reaction mixture was then diluted with dichloromethane (5 mL), treated with water (0.1 mL), NaOH (3*M*, 0.1 mL) and water (0.5 mL) and dried with $MgSO_4$. The mixture was then stirred for a further 15 min and filtered through a pad of Celite™, then concentrated and dried under reduced pressure. The crude product was used in the next step without further purification

To a solution of the crude mixture in acetonitrile (0.5 mL) was added sodium hydride (60% w/w, 9.5 mg, 0.24 mmol) at 0 °C and the mixture was allowed to stir for 5 mins. Allyl bromide (72 μL, 0.83 mmol) was then added and the reaction was allowed to stir at rt until starting material was consumed. The reaction was quenched with a few drops of methanol and concentrated under reduced pressure and the resulting crude mixture was partitioned between ethyl acetate (5 mL) and water (5 mL). The aqueous layer was washed with ethyl acetate (2 × 5 mL) and the combined organic layers were dried with $MgSO_4$, filtered and concentrated under reduced pressure. The resulting crude

mixture was purified by column chromatography (10% ethyl acetate in hexane) to yield ether **122** as a yellow oil in 73% yield from starting ester **119**. $[\alpha]_D^{22}$ +2.8 (*c* 0.25, $CHCl_3$); R_f 0.21 (10% ethyl acetate in hexane); **IR** (film) 3285 (CC-H), 2926, 2854 (C-H), 2120 (C≡C), 1653 (C=C); **^{1}H NMR** (300 MHz, $CDCl_3$) δ 7.74 (2H, d, *J* = 8.4 Hz, Ar-H), 7.26 (2H, d, *J* = 8.1 Hz, Ar-H), 6.28 (1H, dt, *J* = 14.1, 1.2 $H_{1'}$), 5.86 (1H, ddt, *J* = 17.4, 10.5, 5.7 Hz, $H_{6'}$), 5.59 (1H, dt, *J* = 14.1, 6.6 Hz, $H_{2'}$), 5.23 (1H, ddd, *J* = 17.1, 3.3, 1.5 Hz, $H_{7'a}$), 5.16 (1H, ddd, *J* = 10.5, 3.0, 1.5 Hz, $H_{7'b}$), 4.04 (1H, tt, *J* = 7.5, 5.7 Hz, H_2), 3.94 (2H, dd, *J* = 6.3, 1.2 Hz, $H_{3'}$), 3.88 (2H, dt, *J* = 5.7, 1.5 Hz, $H_{5'}$), 3.83-3.72 (2H, m, H_1), 2.61 (1H, ddd, *J* = 17.1, 7.2, 2.7 Hz, H_{3a}), 2.50-2.40 (1H, m H_{3b}), 2.40 (3H, s, Ar-CH_3), 1.84 (1H, t, *J* = 2.7 Hz, H_5), 0.84 (9H, s, $C(CH_3)_3$) 0.01 (3H, s, $SiCH_3$) 0.00 (3H, s, $SiCH_3$); **^{13}C NMR** (75 MHz, $CDCl_3$) δ 143.7, 137.8, 134.7, 129.6, 127.7, 127.0, 118.8, 117.2, 80.5, 70.7, 70.6, 69.0, 63.4, 59.3, 25.9, 21.7, 19.8, 18.3, -5.5; **MS** (ESI+) *m/z* 486 ([M + Na]$^+$, 100%), 502 ([M + K]$^+$, 30%); **HRMS** (ESI+) *m/z* calcd for $C_{24}H_{37}NO_4SSiNa$: 486.2110, found 486.2109, $C_{24}H_{37}NO_4SSiK$: 502.1850, found 502.1853.

The following compounds could not be fully characterised due to the limited amount of material obtained.

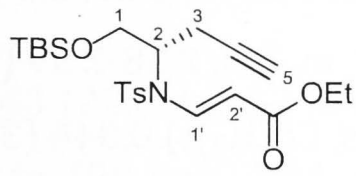
(*S,E*)-allyl 3-(*N*-(1-(*tert*-butyldimethylsilyloxy)-4-methylenehex-5-en-2-yl)-4-methylphenylsulfonamido)acrylate (121)



A solution of enyne **121** (10.9 mg, 23 μmol) in dichloromethane (2.5 mL) was freeze-dried-thawed under an ethylene atmosphere then added Hoveyda-Grubbs catalyst (1.4 mg, 2.2 μmol). The reaction was heated to reflux and allowed to stir at this temperature for 1 h. After this time, the crude reaction mixture was concentrated and purified by preperative thin layer chromatography (eluent 30% ethyl acetate in hexane). A yield was not obtained for this reaction, however the title compound was tentatively identified using **^{1}H NMR** (300 MHz, $CDCl_3$) δ 7.80 (1H, d, *J* = 14.4 Hz, $H_{2'}$), 7.72 (2H, d, *J* = 8.5 Hz, Ar-H), 7.29 (2H, d, *J* = 7.9 Hz, Ar-H), 6.20 (1H, dd, *J* = 17.7, 10.8 Hz, H_5), 5.95 (1H, ddt, *J* = 17.1, 10.2, 5.7 Hz, $H_{6'}$), 5.64 (1H, d, *J* = 14.3 Hz, $H_{1'}$), 5.35 – 5.21 (2H, m, $H_{7'}$), 5.21 (1H, d, *J* = 17.7 Hz, H_{6a}), 5.08 (d, *J* = 10.8 Hz, H_{6b}), 4.93 (1H, d, *J* = 3.5 Hz, $H_{1''}$), 4.63 (2H, d, *J* = 5.6 Hz, $H_{5'}$), 4.40 (1H, m, H_2), 3.82 – 3.66 (2H, m, H_1), 2.77 (1H, dd, *J* = 14.4, 6.8 Hz, H_{3a}), 2.57 (1H, dd, *J* = 13.5, 8.1 Hz, H_{3b}), 2.43 (3H, s, Ar-Me), peaks below 2 ppm were omitted due to presence of water, grease and silicon grease impurities.

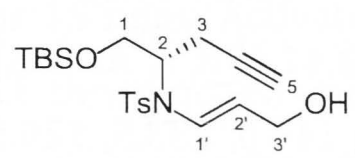
6.3 Experimental procedures for chapter 3

(*S,E*)-Ethyl 3-(*N*-(1-(*tert*-butyldimethylsilyloxy)pent-4-yn-2-yl)-4-methylbenzenesulfonamido)propenoate (146)



To a solution of silyl ether **118** (810 mg, 2.20 mmol) in acetonitrile (16 mL) was added ethyl propiolate (281 mg, 2.86 mmol) and N-methylmorpholine (290 mg, 2.86 mmol) and the reaction mixture was allowed to stir at rt for 16 h. The reaction mixture was concentrated under reduced pressure. The crude mixture was purified by flash chromatography (10% ethyl acetate in hexane) to yield conjugated ester **146** (1.005 g, 98%) as a pale yellow oil. $[\alpha]_D^{20}$ +16.3 (*c* 1.10, $CHCl_3$); $\mathbf{R_f}$ 0.49 (30% ethyl acetate in hexane); **IR** (film) 3291 (CC-H), 3066, 2955, 2930, 2884, 2857 (C-H), 2123 (C≡C), 1712 (C=O), 1623, 1599 (C=C); **^{1}H NMR** (300 MHz, $CDCl_3$) δ 7.78 (1H, d, J = 8.4 Hz, Ar-H), 7.69 (1H, d, *J* = 14.4 Hz, $H_{2'}$), 7.31 (1H, d, J = 8.4 Hz, Ar-H), 5.67 (1H, d, *J* = 14.4 Hz, $H_{1'}$), 4.47-4.38 (1H, m, H_2), 4.14 (2H, q, *J* = 7.2 Hz, $\underline{CH_2}CH_3$), 3.90-3.80 (2H, m, H_1), 2.70 (1H, ddd, *J* = 17.1, 7.5, 2.7 Hz, H_{3a}), 2.70 (1H, ddd, *J* = 17.1, 7.5, 2.7 Hz, H_{3b}), 2.41 (3H, s, Ar-Me), 1.89 (1H, t, *J* = 2.7 Hz, H_5), 1.25 (3H, t, *J* = 7.2 Hz, $CH_2\underline{CH_3}$), 0.84 (9H, s, $C(CH_3)_3$), 0.02 (3H, s, $SiCH_3$), 0.01 (3H, s, $SiCH_3$); **^{13}C NMR** (75 MHz, $CDCl_3$) δ 167.2, 144.8, 139.9, 135.6, 129.8, 127.6, 101.0, 79.3, 71.2, 63.0, 60.0, 59.6, 25.7, 21.5, 19.4, 18.1, 14.3, -5.65, -5.70; **MS** (ESI+) *m/z* 488 ([M + Na]$^+$, 100%), 466 ([M + H]$^+$, 12%); **HRMS** (ESI+) calcd for $C_{23}H_{36}NO_5SSi$: 466.2083, found 466.2092, $C_{23}H_{35}NO_5SSiNa$: 488.1903, found 488.1900.

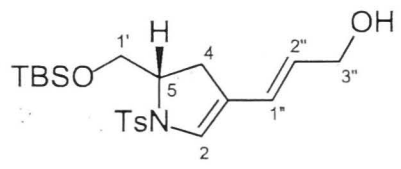
(*S,E*)-*N*-(1-(*tert*-Butyldimethylsilyloxy)pent-4-yn-2-yl)-*N*-(3-hydroxyprop-1-enyl)-4-methylbenzenesulfonamide (142)



To a solution of conjugated ester **146** (511 mg, 1.10 mmol) in dichloromethane (7 mL) was added a solution of diisobutylaluminium hydride in hexanes (1.0 *M*, 4.39 mL, 4.39 mmol) at -78 °C and stirred for 2 h. The reaction mixture was then diluted with dichloromethane (25 mL), treated with water (0.5 mL), NaOH (3 *M*, 0.5 mL) and water (1.5 mL) and dried with $MgSO_4$. The mixture was stirred for a further 15 min and filtered through a pad of Celite™, then concentrated under reduced pressure. The crude mixture

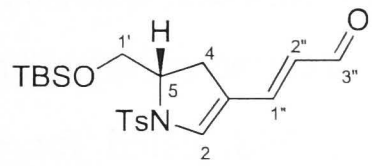
was purified by flash chromatography (20% ethyl acetate in hexane) to yield allylic alcohol **142** (392 mg, 84%) as a pale yellow oil. $[\alpha]_D^{20}$ +1.2 (*c* 0.84, $CHCl_3$); R_f 0.18 (30% ethyl acetate in hexane); **IR** (film) 3435 (O-H), 2956, 2926, 2850 (C-H), 2103 (C≡C), 1644 (C=C); **^{1}H NMR** (300 MHz, $CDCl_3$) δ 7.69 (2H, d, *J* = 8.1 Hz, Ar-H), 7.22 (2H, d, *J* = 8.1 Hz, Ar-H), 6.20 (1H, d, *J* = 13.8, $H_{1'}$), 5.67 (1H, dt, *J* = 14.1, 6.3 Hz, $H_{2'}$), 4.27-4.18 (1H, m, H_2), 4.04 (2H, d, *J* = 6.0 Hz, $H_{3'}$), 3.75-3.64 (2H, m, H_1), 2.58-2.39 (3H, m, H_3, OH), 2.35 (3H, s, Ar-CH_3), 1.81 (1H, t, *J* = 2.4 Hz, H_5) 0.79 (9H, s, $C(CH_3)_3$) 0.044 (3H, s, $SiCH_3$) 0.049 (3H, s, $SiCH_3$); **^{13}C NMR** (75 MHz, $CDCl_3$) δ 143.6, 137.0, 129.5, 127.4, 125.5, 123.0, 80.3, 70.7, 63.2, 61.7, 59.2, 25.7, 21.5, 19.6, 18.1, -5.61, -5.63; **MS** (ESI+) *m/z* 446 ([M + Na]$^+$, 100%); **HRMS** (ESI+) *m/z* calcd for $C_{21}H_{33}NO_4SSiNa$: 446.1797, found 446.1802.

(*S,E*)-3-(5-((*tert*-Butyldimethylsilyloxy)methyl)-1-tosyl-4,5-dihydro-1*H*-pyrrol-3-yl) prop-2-en-1-ol (143)



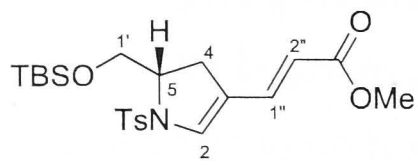
A solution of allylic alcohol **142** (22.9 mg, 54.1 μmol) and *cis*-butene diol (14 μL, 170.0 μmol) in dichloroethane (1 mL) under an argon atmosphere was freezed-thawed-dried and Grubbs 2nd generation catalyst (2.3 mg, 2.7 μmol) added. The reaction mixture was heated to 90 °C and allowed to stir at this temperature for 1 h under an argon atomosphere. The reaction mixture was cooled to rt then adsorbed on to silica and purified by flash chromatography (20% ethyl acetate in hexane) to yield dihydropyrrole **143** (14.0 mg, 63.2%) as a yellow oil. $[\alpha]_D^{20}$ -144.1 (*c* 0.57, $CHCl_3$); R_f 0.24 (30% ethyl acetate in hexane); **IR** (film) 3421 (O-H), 2952, 2928, 2853 (C-H), 1654, 1647, 1636 (C=C); **^{1}H NMR** (300 MHz, $CDCl_3$) δ 7.64 (2H, d, *J* = 8.1 Hz, Ar-H), 7.29 (2H, d, *J* = 7.8 Hz, Ar-H), 6.36-6.31 (2H, m, H_2 & $H_{1''}$), 5.52 (1H, dt, *J* = 15.6, 6.0 Hz, $H_{2''}$), 4.17 (2H, d, *J* = 5.7 Hz, $H_{3''}$), 3.89 (1H, dd, *J* = 9.9, 3.9 Hz, $H_{1'a}$), 3.77 (1H, m, H_5), 3.65 (1H, dd, *J* = 9.6, 7.8 Hz, $H_{1'b}$), 2.68-2.49 (2H, m, H_4), 2.43 (1H, s, OH), 2.41 (3H, s, Ar-CH_3), 0.87 (9H, s, $C(CH_3)_3$), 0.07 (6H, s, $SiCH_3$); **^{13}C NMR** (75 MHz, $CDCl_3$) δ 144.0, 133.5, 129.8, 128.6, 128.0, 127.4, 124.6, 124.3, 65.3, 63.2, 61.0, 32.5, 25.9, 21.6, 18.2, -5.3; **MS** (ESI+) *m/z* 446 ([M + Na]$^+$, 100%); **HRMS** (ESI+) *m/z* calcd for $C_{21}H_{33}NO_4SSiNa$: 446.1797, found 446.1798.

(*S,E*)-3-(5-((*tert*-Butyldimethylsilyloxy)methyl)-1-tosyl-4,5-dihydro-1*H*-pyrrol-3-yl) propenal (147)



A solution of allylic alcohol **143** (22.0 mg, 52 μmol) in dichloromethane (3 mL) was added activated manganese dioxide (90 mg, 1.04 mmol) at room temperature. The reaction mixture was allowed to stir at this temperature for 1 h. The reaction mixture was then filtered through a pad of Celite™ and the filtrate was concentrated under reduced pressure to yield crude aldehyde **147** as a clear, colourless oil. The crude mixture was used in the next reaction without further purification. **^{1}H NMR** (300 MHz, $CDCl_3$) δ 9.52 (1H, d, J = 7.8 Hz, $H_{3''}$), 7.67 (2H, d, J = 8.4 Hz, Ar-H), 7.34 (2H, d, J = 8.4 Hz, Ar-H), 7.21 (1H, d, J = 15.3 Hz, $H_{1''}$), 6.91 (1H, s, H_2), 5.85 (1H, dd, J = 15.3, 7.8 Hz, $H_{2''}$), 3.94 (1H, m, H_5), 3.86 (1H, dd, J = 10.2, 3.3 Hz, $H_{1'a}$), 3.79 (1H, dd, J = 10.2, 6.3 Hz, $H_{1'b}$), 2.66 (2H, m, H_4), 2.44 (3H, s, Ar-CH_3), 0.85 (9H, s, $C(CH_3)_3$), 0.06 (6H, s, $SiCH_3$); **MS** (ESI+) m/z 460 ($[M + K]^+$, 100%), 444 ($[M + Na]^+$, 100%); **HRMS** (ESI+) m/z calcd for $C_{21}H_{31}NO_4SSiNa$: 444.1641, found 444.1643; the full characterisation of this compound was not carried out due to the limited material available and possible instability.

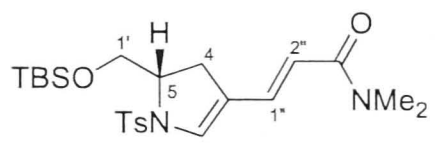
(*S,E*)-Methyl 3-(5-((*tert*-butyldimethylsilyloxy)methyl)-1-tosyl-4,5-dihydro-1*H*-pyrrol-3-yl)propenoate (150)



A solution of aldehyde **147** (52 μmol) in methanol (3 mL) was added sodium cyanide (12.7 mg, 0.26 mmol) and a drop of glacial acetic acid at room temperature and the reaction was allowed to stir for 15 mins. Activated manganese dioxide (82 mg, 0.94 mmol) was then added at rt and the reaction mixture was allowed to stir at this temperature for 1 h. The reaction mixture was then filtered through a pad of Celite™ and washed with methanol (10 mL). The filtrate was concentrated under reduced pressure and the resulting crude material was purified by flash chromatography to yield methyl ester **150** (10.6 mg, 45%) as a yellow oil. $[\alpha]_D^{20}$ -159.1 (c 0.09, $CHCl_3$); **R_f** 0.14 (10% ethyl acetate in hexane); **IR** (film) 2949, 2928, 2852 (C-H), 1716 (C=O), 1623, 1596 (C=C); **^{1}H NMR** (300 MHz, $CDCl_3$) δ 7.65 (2H, d, J = 8.4 Hz, Ar-H), 7.38 (1H, d, J = 15.3 Hz, $H_{1''}$), 7.32 (2H, d, J = 8.4 Hz, Ar-H), 6.74 (1H, s, H_2), 5.55 (1H, d, J = 15.3 Hz, $H_{2''}$), 3.89-3.85 (2H, m,

$H_{1'}$), 3.77-3.71 (1H, m, H_5), 3.73 (1H, s, OCH_3), 2.67-2.51 (2H, m, H_4), 2.43 (1H, s, Ar-CH_3), 0.86 (9H, s, $C(CH_3)_3$), 0.07 (6H, s, $SiCH_3$); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 167.6, 144.5, 138.0, 135.8, 134.0, 130.1, 127.4, 122.5, 116.6, 65.1, 61.9, 51.7, 32.0, 25.9, 21.8, 18.3, -5.2; **MS** (ESI+) *m/z* 452 ([M + H]$^+$, 45%), 474 ([M + Na]$^+$, 100%); **HRMS** (ESI+) *m/z* calcd for $C_{22}H_{34}NO_5SSi$: 452.1927, found 452.1938, calcd for $C_{22}H_{33}NO_5SSiNa$: 474.1746, found 474.1755.

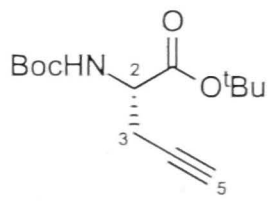
(*S,E*)-3-(5-((*tert*-Butyldimethylsilyloxy)methyl)-1-tosyl-4,5-dihydro-1*H*-pyrrol-3-yl)-*N,N*-dimethylpropenamide (149)



2

To a solution of ester **150** (10.6 mg, 23 μmol) and dimethylamine hydrochloride (3.8 mg, 47 μmol) in THF (2 mL) was added dropwise isopropylmagnesium chloride (2 M in THF, 59 μL, 117 μmol) over 1 min at -78 °C. The reaction mixture was allowed to stir at this temperature for 3 h. The reaction mixture was then treated with phosphate buffer (pH = 4, 5 mL) and extracted with ethyl acetate (3 × 5 mL). The combined organic extracts were dried with $MgSO_4$, filtered and concentrated under reduced pressure. The crude material was purified by flash chromatography (50% ethyl acetate in hexane) to yield dimethylamide **149** (2.0 mg, 18%) as a yellow oil. **^{1}H NMR** (300 MHz, $CDCl_3$) δ 7.65 (2H, d, *J* = 8.4 Hz, Ar-H), 7.36 (1H, d, *J* = 15.0 Hz, $H_{1''}$), 7.31 (2H, d, *J* = 8.1 Hz, Ar-H), 6.68 (1H, s, $H_{2''}$), 5.96 (1H, d, *J* = 15.0 Hz, $H_{2''}$), 3.92-3.71 (3H, m, $H_{1'}$ & H_5), 3.04 (1H, s, NCH_3), 3.00 (1H, s, NCH_3), 2.66-2.52 (2H, m, H_4), 2.42 (1H, s, Ar-CH_3), 0.87 (9H, s, $C(CH_3)_3$), 0.08 (6H, s, $SiCH_3$); the full characterisation of this compound was not carried out due to the limited material available.

(S)-*tert*-Butyl 2-(*tert*-butoxycarbonylamino)pent-4-ynoate (155)

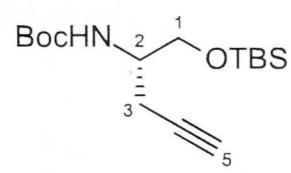


To a solution of imine **98** (4.01 mmol) in tetrahydrofuran (35 mL) was added aqueous citric acid (30% w/v, 7.7 mL, 12.0 mmol), and the mixture was stirred at rt for 20 h. The reaction mixture was then concentrated under reduced pressure, diluted with

diethyl ether (25 mL) and extracted twice with hydrochloric acid (1 *M*, 3 × 25 mL). The combined aqueous layers were basified to pH ~8-9 with solid sodium bicarbonate and extracted with ethyl acetate (3 × 50 mL). The combined organic layers were dried with $MgSO_4$, filtered and concentrated under reduced pressure to afford a light brown oil.

To a solution of the above oil in dioxane:water (1:1, 30 mL) was added Boc anhydride (1.75 g, 8.02 mmol) and sodium bicarbonate (1.01 g, 12.03 mmol) at rt and the reaction was allowed to stir for 16 h. The reaction mixture was then concentrated under reduced pressure and extracted with ethyl acetate (3 × 25 mL). The combined organic layers were dried with $MgSO_4$, filtered and concentrated under reduced pressure to afford a brown oil. The crude mixture was purified by flash chromatography (gradient elution of 5-10% ethyl acetate in hexane) to yield ester **117** (857.1 mg, 79%, 95% *ee*) from imine **98** as a white solid (m.p. 61-62 °C). $[\alpha]_D^{20}$ +33.6 (*c* 0.63, $CHCl_3$); R_f 0.41 (10% ethyl acetate in hexane); **IR** (film) 3748 (NH), 3312 (CC-H), 2979, 2933 (C-H), 2123 (C≡CH), 1735, 1717 (C=O); **^{1}H NMR** (400 MHz, $CDCl_3$) δ 5.34 (1H, d, *J* = 6.8 Hz, NH), 4.36-4.32 (1H, m, H_2), 2.75-2.66 (2H, m, H_3), 2.01 (1H, s, H_5), 1.48 (9H, s, $C(CH_3)_3$), 1.45 (9H, s, $C(CH_3)_3$); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 169.8, 163.1, 82.6, 80.1, 79.0, 71.4, 52.4, 28.5, 28.1, 23.2; **MS** (ESI+) *m/z* 292 ($[M + Na]^+$, 50%); **HRMS** (ESI+) calcd for $C_{14}H_{24}NO_4$: 270.1705, found 270.1703, calcd for $C_{14}H_{23}NO_4Na$: 292.1525, found 292.1525.

(S)-*tert*-Butyl 1-(*tert*-butyldimethylsilyloxy)pent-4-yn-2-ylcarbamate (156)



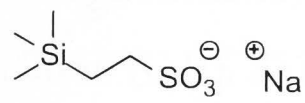
To a solution of ester **155** (305.5 mg, 1.13 mmol) in tetrahydrofuran (20 mL) was added lithium aluminium hydride (174 mg, 4.58 mmol) at 0 °C and the reaction was warmed to rt and stirred for 3 h. The reaction mixture was then cooled to 0 °C and diluted with diethyl ether (75 mL), treated with water (0.2 mL), NaOH (3 *M*, 0.2 mL) and water (0.6 mL), and dried with $MgSO_4$. The mixture was then stirred for a further 15 min and filtered through a pad of Celite™, then concentrated under reduced pressure. The crude mixture was used in the next reaction without further purification.

A solution of the above crude mixture in dichloromethane (10 mL) was added *tert*-butyldimethylsilyl chloride (230.6 mg, 1.53 mmol), imidazole (104.2 mg, 1.53 mmol) and DMAP (12.5 mg, 0.10 mmol) and the reaction was stirred at rt for 16 h. The reaction mixture was added water (10 mL) and extracted with dichloromethane (2 × 20 mL). The

combined organic layers were dried with $MgSO_4$, filtered and concentrated under reduced pressure. The crude mixture was purified by flash chromatography (gradient elution of 5-10% ethyl acetate in hexane) to yield silyl ether **156** (284.5 mg, 80% from ester **155**) as a clear, colourless oil. $[\alpha]_D^{20}$ -1.7 (*c* 0.294, $CHCl_3$); **IR** (film) 3312 (CC-H), 2955, 2929, 2857 (C-H), 2121 (C≡CH), 1718 (C=O); **^{1}H NMR** (400 MHz, $CDCl_3$) δ 4.82 (1H, d, *J* = 5.6 Hz, NH), 3.76 (2H, dd, *J* = 10.0, 3.2 Hz, H_1), 3.60 (1H, dd, *J* = 10.0, 5.6 Hz, H_2), 2.51-2.37 (2H, m, H_3), 1.96 (1H, t, *J* = 2.8 Hz, H_5), 1.44 (9H, s, $C(CH_3)_3$), 0.89 (9H, s, $C(CH_3)_3$), 0.07 (6H, s, $Si(CH_3)_2$); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 155.4, 80.8, 79.6, 70.4, 63.1, 50.5, 28.5, 26.0, 21.1, 18.4, -5.3; **MS** (ESI+) *m/z* 336 ($[M + Na]^+$, 80%); **HRMS** (ESI+) calcd for $C_{16}H_{32}NO_3Si$: 314.2151, found 314.2149, calcd for $C_{16}H_{31}NO_3SiNa$: 336.1971, found 336.1958, calcd for $C_{16}H_{31}NO_3SiK$: 352.1710, found 352.1711.

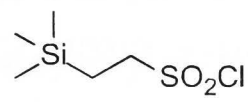
6.4 Experimental procedures for chapter 4

Sodium 2-(trimethylsilyl)ethanesulfonate (160)[69]



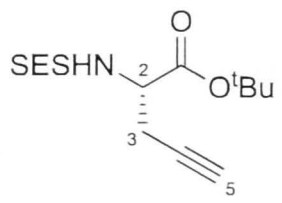
Following a procedure reported by Weinreb and co-workers,[69] a solution of vinyl trimethylsilane (9.35 mL, 64.3 mmol) in methanol (100 mL) was added dropwise *tert*-butyl peroxybenzoate (245 µL, 1.29 mmol) and a solution of sodium hydrogen sulphite (13.4 g, 129 mmol) in water (100 mL) at rt. The reaction mixture was warmed to 50 °C and stirred for 48 h. The reaction was cooled to rt and added methanol (50 mL) and concentrated under reduced pressure. In order to remove water from the solution, the resultant mixture diluted with methanol (100 mL) and concentrated under reduced pressure. This was repeated a further two times to yield a white solid. Methanol (200 mL) was added and the suspension was stirred vigorously for 15 min. The mixture was filtered through a pad of Celite™, and the collected solids were again taken up into methanol (100mL). This was repeated a further two times and the combined filtrate was concentrated under reduced pressure to yield a white solid. The solid was further dried in the oven at 110 °C overnight to yield sulfonate **160** as a white solid (11.7 g, 89%). The spectroscopic data obtained for this compound correlated with that previously reported.[69]

2-(Trimethylsilyl)ethanesulfonyl chloride (161)[69]



Following a procedure reported by Weinreb and co-workers,[70] a suspension of sulfonate **160** (11.7 g, 57.2 mmol) in dichloromethane (200 mL) was added phosphorus pentachloride (35.7 g, 172 mmol) in 1g portions over 10 mins at 0 °C. The reaction was allowed to stir at this temperature for 90 min. The reaction was quenched by pouring over ice (150 mL) and the resulting mixture was allowed to stir for a further 30 min. The reaction mixture was separated and the aqueous layer was extracted with dichloromethane (3 × 150 mL). The combined organic layers were washed with saturated sodium bicarbonate (3 × 150 mL) and brine (150 mL). The organic phase was dried over $MgSO_4$, filtered and concentrated under reduced pressure to yield a pale brown oil. The crude mixture was purified by flash chromatography (100% hexane) to yield sulfonyl chloride **161** as a pale brown oil (6.9 g, 60%). The spectroscopic data obtained for this compound correlated with that previously reported.[69]

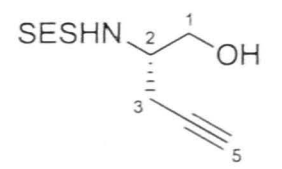
(*S*)-*tert*-Butyl 2-(2-(trimethylsilyl)ethylsulfonamido)pent-4-ynoate (162)



To a solution of imine **98** (11.98 mmol) in tetrahydrofuran (100 mL) was added aqueous citric acid (30% w/v, 23.0 mL, 35.9 mmol), and the mixture was stirred at rt for 20 h. The reaction mixture was then concentrated under reduced pressure, diluted with diethyl ether (75 mL) and extracted twice with hydrochloric acid (1*M*, 3 × 75 mL). The combined aqueous layers were basified to pH ~8-9 with solid sodium bicarbonate and extracted with ethyl acetate (6 × 100 mL). The combined organic layers were dried with $MgSO_4$, filtered and concentrated under reduced pressure to afford a light brown oil.

To a solution of the above oil in acetonitrile (25 mL) was added triethylamine (5.05 mL, 35.9 mmol) then 2-(trimethylsilyl)ethanesulfonyl chloride (3.13 g, 15.57 mmol) at 0 °C and the reaction was stirred for 16 h. The reaction mixture was concentrated under reduced pressure and extracted with ethyl acetate (3 × 50 mL). The combined organic layers were dried with $MgSO_4$, filtered and concentrated under reduced pressure to afford a light brown oil. The crude mixture was purified by flash chromatography (gradient elution of 5-10% ethyl acetate in hexane) to yield ester **162** (2.46 g, 62%, 98% *ee*) from imine **98** as a pale yellow oil. $\mathbf{R_f}$ 0.19 (10% ethyl acetate in hexane); $[\boldsymbol{\alpha}]_{\mathbf{D}}^{\mathbf{20}}$ +6.1 (*c* 0.98, $CHCl_3$); **IR** (film) 3278 (N-H), 2978, 2955, 2930, 2854 (C-H), 2124 (C≡CH), 1734 (C=O); **^{1}H NMR** (400 MHz, $CDCl_3$) δ 5.21 (1H, d, *J* = 8.8 Hz, NH), 4.13 (1H, dt, *J* = 8.8, 4.8 Hz, H_2), 2.92 (2H, m, CH_2SO_2), 2.72 (1H, m, H_{3a}), 2.64 (1H, m, H_{3b}), 2.04 (1H, t, *J* = 2.8 Hz, H_5), 1.44 (9H, s, $C(CH_3)_3$), 1.04 (2H, m, CH_2Si), -0.05 (9H, s, $Si(CH_3)_3$); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 169.2, 83.2, 78.4, 72.1, 54.7, 50.3, 27.8, 24.4, 10.3, -2.1; **MS** (ESI+) *m/z* 356 ([M + Na]$^+$, 100%); **HRMS** (ESI+) calcd for $C_{14}H_{27}NO_4SSiNa$: 356.1328, found 356.1331

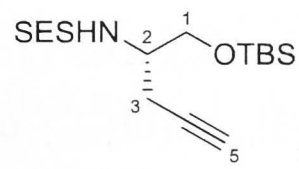
(*S*)-*N*-(1-Hydroxypent-4-yn-2-yl)-2-(trimethylsilyl)ethanesulfonamide (202)



To a solution of ester **162** (3.03 g, 9.08 mmol) in diethyl ether (125 mL) was added lithium aluminium hydride (1.03 g, 27.3 mmol) at 0 °C and the reaction stirred at rt for 3 h. The reaction mixture was then cooled to 0 °C and diluted with diethyl ether (125 mL), treated with water (1 mL), NaOH (3*M*, 1 mL) and water (3 mL), and dried with $MgSO_4$. The

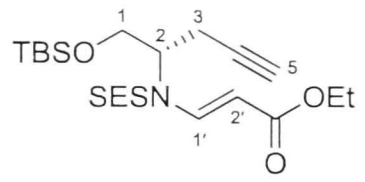
mixture was stirred for a further 15 min and filtered through a pad of Celite™, then concentrated under reduced pressure. The crude mixture was purified by flash chromatography (30% ethyl acetate in hexane) to yield alcohol **202** (1.93 g, 81%) as a pale yellow oil. $\mathbf{R_f}$ 0.22 (30% ethyl acetate in hexane); $[\alpha]_D^{20}$ +15.2 (*c* 0.45, $CHCl_3$); **IR** (film) 3489 (O-H), 3287 (N-H), 2953, 2924, 2854 (C-H), 2120 (C≡CH); **^{1}H NMR** (400 MHz, $CDCl_3$) δ 5.14 (1H, d, *J* = 8.8 Hz, NH), 3.73 (2H, m, H_1), 3.59 (1H, m, H_2), 3.01 (2H, m, CH_2SO_2), 2.95 (1H, m, OH), 2.54 (1H, m, H_{3a}), 2.52 (1H, m, H_{3b}), 2.06 (1H, t, *J* = 2.8 Hz, H_5), 1.06 (2H, m, CH_2Si), 0.05 (9H, s, $Si(CH_3)_3$); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 80.0, 71.6, 64.6, 54.0, 50.3, 22.6, 10.7, -1.8; **MS** (ESI+) *m/z* 286 ($[M + Na]^+$, 100%); **HRMS** (ESI+) calcd for $C_{10}H_{21}NO_3SSiNa$: 286.0909, found 286.0906

(*S*)-*N*-(1-(*tert*-Butyldimethylsilyloxy)pent-4-yn-2-yl)-2-(trimethylsilyl)ethanesulfonamide (163)



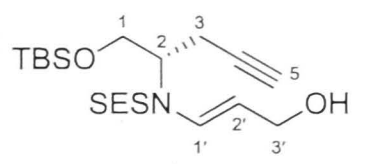
To a solution of alcohol **202** (1,24 g, 4.90 mmol) in dichloromethane (100 mL) was added *tert*-butyldimethylsilyl chloride (1.11 g, 7.36 mmol), imidazole (0.501 g, 7.36 mmol) and DMAP (30 mg, 0.246 mmol) and the reaction was stirred at rt for 16 h. The reaction mixture was added water (50 mL) and extracted with dichloromethane (2 × 50 mL). The combined organic layers were dried with $MgSO_4$, filtered and concentrated under reduced pressure. The crude mixture was purified by flash chromatography (gradient elution of 5-10% ethyl acetate in hexane) to yield silyl ether **163** (1.39 g, 77%) as a white solid (**m.p.** 92-95 °C). $\mathbf{R_f}$ 0.64 (30% ethyl acetate in hexane); $[\alpha]_D^{20}$ -1.5 (*c* 0.35, $CHCl_3$); **IR** (film) 3315 (CC-H), 3235 (N-H), 2953, 2930, 2857 (C-H), 2123 (C≡CH); **^{1}H NMR** (400 MHz, $CDCl_3$) δ 4.62 (1H, d, *J* = 8.7 Hz, NH), 3.77 (1H, dd, *J* = 9.8, 4.0 Hz, H_{1a}), 3.66 (1H, dd, *J* = 10.0, 5.2 Hz, H_{1b}), 3.55 (1H, m, H_2), 2.97 (2H, m, CH_2SO_2), 2.55 (1H, m, H_{3a}), 2.48 (1H, m, H_{3b}), 2.01 (1H, t, *J* = 2.8 Hz, H_5), 1.05 (2H, m, CH_2Si), 0.88 (9H, s, $C(CH_3)_3$), 0.072 (3H, s, $SiCH_3$), 0.069 (3H, s, $SiCH_3$), 0.04 (9H, s, $Si(CH_3)_3$); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 80.2, 71.2, 64.1, 53.8, 50.2, 25.9, 22.4, 18.4, 10.7, -1.9 (2C), -5.4; **MS** (ESI+) *m/z* 400 ($[M + Na]^+$, 100%); **HRMS** (ESI+) calcd for $C_{16}H_{35}NO_3SSi_2Na$: 400.1774, found 400.1779

(*S,E*)-Ethyl 3-(*N*-(1-(*tert*-butyldimethylsilyloxy)pent-4-yn-2-yl)-2-(trimethylsilyl)ethylsulfonamido)acrylate (164)



To a solution of silyl ether **163** (1.24 g, 3.28 mmol) in acetonitrile (25 mL) was added ethyl propiolate (0.418 g, 4.27 mmol) and *N*-methylmorpholine (0.431 g, 4.27 mmol) and the reaction was allowed to stir at rt for 16 h. The reaction mixture was concentrated under reduced pressure to yield a brown oil. The crude mixture was purified by flash chromatography (10% ethyl acetate in hexane) to yield conjugated ester **164** (1.44 g, 92%) as a pale yellow oil. $\mathbf{R_f}$ 0.24 (10% ethyl acetate in hexane); $[\alpha]_D^{20}$ -1.0 (*c* 0.96, $CHCl_3$); **IR** (film) 3311 (CC-H), 2954, 2927, 2854 (C-H), 1712 (C=O), 1623 (C=C); **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.67 (1H, d, *J* = 14.3 Hz, $H_{2'}$), 5.54 (1H, d, *J* = 14.3 Hz, $H_{1'}$), 4.27 (1H, m, H_2), 4.17 (2H, q, *J* = 7.2 Hz, CO_2CH_2), 3.91 (1H, m, H_{1a}), 3.85 (1H, m, H_{1b}), 3.19 (2H, m, CH_2SO_2), 2.71 (1H, m, H_{3a}), 2.70 (1H, m, H_{3b}), 2.03 (1H, t, *J* = 2.8 Hz, H_5), 1.26 (3H, t, *J* = 7.2 Hz, CH_3), 1.08 (2H, m, CH_2Si–), 0.87 (9H, s, $C(CH_3)_3$), 0.06 (3H, s, $SiCH_3$), 0.05 (3H, s, $SiCH_3$), 0.04 (9H, s, $Si(CH_3)_3$); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 167.4, 141.2, 99.9, 80.2, 71.5, 63.2, 60.2, 60.1, 49.9, 25.9, 19.8, 18.3, 14.5, 9.8, -1.8 (2C), -5.4; **MS** (ESI+) *m/z* 498 ($[M + Na]^+$, 100%); **HRMS** (ESI+) calcd for $C_{21}H_{42}NO_5SSi_2$: 476.2322, found 476.2330

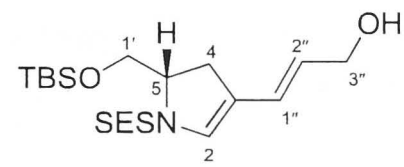
(*S,E*)-*N*-(1-(*tert*-Butyldimethylsilyloxy)pent-4-yn-2-yl)-*N*-(3-hydroxyprop-1-enyl)-2-(trimethylsilyl)ethanesulfonamide (165)



To a solution of conjugated ester **164** (1.12 g, 2.36 mmol) in dichloromethane (47 mL) was added a solution of diisobutylaluminium hydride in hexanes (1.0*M*, 9.44 mL, 9.44 mmol) at -78 °C, then warmed to 0 °C and stirred for 2 h. The reaction mixture was then diluted with dichloromethane (50 mL), treated with water (0.5 mL), NaOH (3*M*, 0.5 mL) and water (1.5 mL) and dried with $MgSO_4$. The mixture was then stirred for a further 15 min and filtered through a pad of Celite™, then concentrated under reduced pressure. The crude mixture was purified by flash chromatography (20% ethyl acetate in hexane) to yield allylic alcohol **165** (0.92 g, 89%) as a pale yellow oil. $\mathbf{R_f}$ 0.24 (20% ethyl acetate in hexane); $[\alpha]_D^{20}$ -1.7 (*c* 1.34, $CHCl_3$); **IR** (film) 3410 (O-H), 3310 (CC-H), 2953, 2928, 2856 (C-H), 1655 (C=C); **^{1}H NMR** (400 MHz, $CDCl_3$) δ 6.40 (1H, dd, *J* = 14.1, 1.2 Hz, $H_{1'}$), 5.59 (1H,

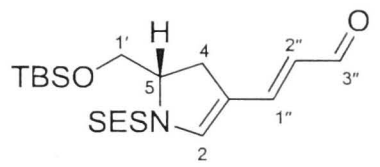
dt, J = 14.1, 6.4 Hz, $H_{2'}$), 4.20-4.12 (3H, m, H_2, $H_{3'}$), 3.85 (1H, m, H_{1a}), 3.80 (1H, m, H_{1b}), 3.11 (2H, m, CH_2SO_2), 2.65-2.62 (2H, m, H_3), 2.02 (1H, t, J = 2.8 Hz, H_5), 1.60 (1H, s, OH), 1.07 (2H, m, CH_2Si), 0.88 (9H, s, $C(CH_3)_3$), 0.059 (3H, s, $SiCH_3$), 0.056 (3H, s, $SiCH_3$), 0.03 (9H, s, $Si(CH_3)_3$); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 127.6, 117.2, 81.1, 71.0, 63.5, 62.3, 59.6, 49.4, 26.0, 20.0, 18.3, 10.1, -1.8 (2C), -5.3; **MS** (ESI+) *m/z* 456 ([M + Na]$^+$, 100%); **HRMS** (ESI+) *m/z* calcd for $C_{21}H_{39}NO_5SSi_2Na$: 456.2036, found 456.2035

(*S,E*)-3-(5-((*tert*-Butyldimethylsilyloxy)methyl)-1-(2-(trimethylsilyl)ethylsulfonyl)-4,5-dihydro-1*H*-pyrrol-3-yl)prop-2-en-1-ol (166)



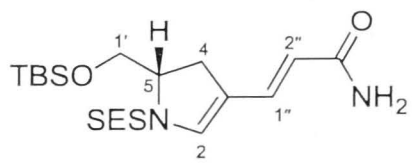
A solution of allylic alcohol **165** (53.1 mg, 0.12 mmol) and allyl alcohol (17μL, 0.24 mmol) in dichloroethane (10 mL) under an argon atmosphere was freezed-thawed-dried and Grubbs 2nd generation catalyst (5.2 mg, 6.1 μmol) was added. The reaction mixture was allowed to stir at 90 °C for 1 h under an argon atomosphere. The crude mixture was then adsorbed on to silica and purified by flash chromatography (20% ethyl acetate in hexane) to yield dihydropyrrole **166** (40.2 mg, 76 %) as a yellow oil. $[\alpha]_D^{20}$ -63.5 (*c* 0.50, $CHCl_3$); **R_f** 0.22 (20% ethyl acetate in hexane); **IR** (film) 3431 (O-H), 2953, 2928, 2856 (C-H), 1648 (C=C); **^{1}H NMR** (400 MHz, $CDCl_3$) δ 6.31 (1H, d, J = 15.6 Hz, $H_{1''}$), 6.21 (1H, s, H_2), 5.57 (1H, dt, J = 15.6, 5.6 Hz, $H_{2''}$), 4.18-4.11 (3H, m, H_5, $H_{3''}$), 3.76 (1H, dd, J = 10.2, 4.2 Hz, $H_{1'a}$), 3.56 (1H, dd, J = 9.8, 7.4 Hz, $H_{1'b}$), 2.93-2.89 (2H, m, CH_2SO_2), 2.86 (1H, m, H_{4a}), 2.62 (1H, dd, J = 15.8, 4.6 Hz, H_{4b}) 2.17 (1H, s, OH), 1.00-0.95 (2H, m, CH_2Si), 0.83 (9H, s, $C(CH_3)_3$), 0.02 (6H, s, $Si(CH_3)_2$), 0.00 (9H, s, $Si(CH_3)_3$); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 128.2, 128.1, 124.4, 122.4, 65.3, 63.2, 61.7, 47.4, 32.6, 25.9, 18.2, 10.0, -2.0, -5.31, -5.35; **MS** (ESI+) *m/z* 456 ([M + Na]$^+$, 100%); **HRMS** (ESI+) *m/z* calcd for $C_{21}H_{39}NO_4SSi_2Na$: 456.2036, found 456.2033

(*S,E*)-3-(5-((*tert*-Butyldimethylsilyloxy)methyl)-1-(2-(trimethylsilyl)ethylsulfonyl)-4,5-dihydro-1*H*-pyrrol-3-yl)propenal (168)



To a solution of dihydropyrrole (64.5 mg, 149 μmol) **166** in dichloromethane (5 mL) was added manganese dioxide (259 mg, 2.97 mmol) at rt and the mixture was stirred at this temperature for 1 h. The reaction mixture was filtered through a pad of Celite™ and washed with dichlormethane (20 mL). The filtrate was concentrated under reduced pressure to yield a yellow oil which was used in the next step without purification. The crude mixture can be purified by flash chromatography (gradient elution 10%-20% ethyl acetate in hexane) to yield aldehyde **168** (58.1 mg, 90%) as a pale yellow solid. (**m.p.** 93-111 °C). $\mathbf{R_f}$ 0.56 (30% ethyl acetate in hexane); $[\boldsymbol{\alpha}]_{\mathbf{D}}^{\mathbf{20}}$ -84.5 (*c* 0.39, $CHCl_3$); **IR** (film) 2949, 2928, 2892, 2855 (C-H), 1669 (C=O), 1610, 1585 (C=C); **^{1}H NMR** (400 MHz, $CDCl_3$) δ 9.54 (1H, d, *J* = 8.0 Hz, $H_{3''}$), 7.23 (1H, d, *J* = 15.6 Hz, $H_{1''}$), 6.83 (1H, s, H_2), 5.93 (1H, dd, *J* = 15.2, 7.6 Hz, $H_{2''}$), 4.37 (1H, app. dq, *J* = 10.8, 4.8, H_5), 3.78 (2H, d, *J* = 4.8, $H_{1'}$), 3.76 (1H, dd, *J* = 10.2, 4.2 Hz, $H_{1'a}$), 3.09-3.03 (2H, m, CH_2SO_2), 2.98 (1H, m, H_{4a}), 2.75 (1H, dd, *J* = 15.6, 4.8 Hz, H_{4b}), 1.06-1.02 (2H, m, CH_2Si) 0.87 (9H, s, $C(CH_3)_3$), 0.07 (6H, s, $SiCH_3$), 0.06 (9H, s, $Si(CH_3)_3$); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 193.2, 145.5, 138.3, 126.9, 120.1, 64.8, 63.0, 49.9, 32.0, 25.9, 18.3, 10.3, -1.9, -5.2, -5.3; **MS** (ESI+) *m/z* 454 ($[M + Na]^+$, 45%); **HRMS** (ESI+) *m/z* calcd for $C_{19}H_{38}NO_4SSi_2$: 432.2060, found 432.2061; $C_{19}H_{37}NO_4SSi_2Na$: 454.1880, found 454.1888

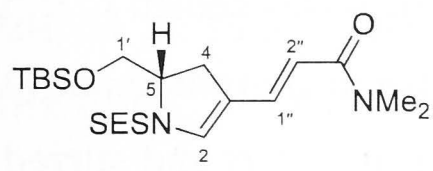
(*S,E*)-3-(5-((*tert*-Butyldimethylsilyloxy)methyl)-1-(2-(trimethylsilyl)ethylsulfonyl)-4,5-dihydro-1*H*-pyrrol-3-yl)propenamide (172)



A suspension of sodium cyanide (41.7 mg, 851 μmol) in isopropanol (5 mL) was charged with ammonia for 5 min at 0 °C. Then, the resulting mixture was added a solution of aldehyde **168** (170 μmol) in dichloromethane (1 mL), followed by activated manganese dioxide (296 mg, 3.40 mmol) at 0 °C. The reaction mixture was allowed to warm up to room temperature and stir for 14 h. The mixture was then filtered through a pad of Celite™ and concentrated under reduced pressure. The crude mixture was then purified by flash chromatography (gradient elution: 60% to 80% ethyl acetate in hexane) to yield

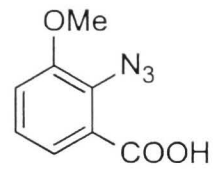
acrylamide **172** (56.9 mg, 75 %) as a yellow oil. $\mathbf{R_f}$ 0.12 (50% ethyl acetate in hexane); $[\alpha]_D^{20}$ -128.3 (*c* 0.23, $CHCl_3$); **IR** (film) 3443, 3350, 3189 (N-H), 2953, 2928, 2856 (C-H), 1663 (C=O), 1629, 1598 (C=C); **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.36 (1H, d, *J* = 14.8 Hz, $H_{1''}$), 6.63 (1H, s, H_2), 5.65 (1H, d, *J* = 15.2 Hz, $H_{2''}$), 5.48 (2H, s, NH_2), 4.29 (1H, ddt, *J* = 10.4, 6.4, 4.4 Hz, H_5), 3.81 (1H, dd, *J* = 10.2, 3.8 Hz, $H_{1'a}$), 3.70 (1H, dd, *J* = 10.2, 6.6 Hz, $H_{1'b}$), 3.03-2.99 (2H, m, CH_2SO_2), 2.95 (1H, m, H_{4a}), 2.70 (1H, dd, *J* = 2.8 Hz, H_{4b}), 1.04-1.00 (2H, m, CH_2Si), 0.87 (9H, s, $C(CH_3)_3$), 0.07 (6H, s, $SiCH_3$), 0.05 (9H, s, $Si(CH_3)_3$); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 168.0, 135.8, 135.6, 120.2, 117.8, 65.1, 62.6, 49.1, 32.2, 26.0, 18.4, 10.3, -1.8, -5.16, -5.23; **MS** (ESI+) *m/z* 469 ($[M + Na]^+$, 100%); **HRMS** (ESI+) *m/z* calcd for $C_{19}H_{38}N_2O_4SSi_2Na$: 469.1989, found 469.1989

(*S,E*)-3-(5-((*tert*-Butyldimethylsilyloxy)methyl)-1-(2-(trimethylsilyl)ethylsulfonyl)-4,5-dihydro-1*H*-pyrrol-3-yl)-*N,N*-dimethylpropenamide (171)



To a solution of acrylamide **172** (26.2 mg, 59 μmol) in tetrahydrofuran (1 mL) was added sodium hydride (60% wt, 12 mg, 300 μmol) and iodomethane (19 μL, 304 μmol) at 0 °C. The reaction mixture was allowed to stir for 1 h, then it was treated with a few drops of methanol and concentrated under reduced pressure. The crude mixture was then partitioned between dichloromethane (10 mL) and water (10 mL) and the aqueous phase was extracted with dichloromethane (2 × 10 mL). The combined organic phases were dried with $MgSO_4$ and concentrated under reduced pressure. The crude material was then purified by flash chromatography (gradient elution: 40% to 70% ethyl acetate in hexane) to yield dimethylacrylamide **171** (23.6 mg, 85 %) as a yellow oil. $\mathbf{R_f}$ 0.18 (50% ethyl acetate in hexane); $[\alpha]_D^{20}$ -92.4 (*c* 0.15, $CHCl_3$); **IR** (film) 2953, 2927, 2855 (C-H), 1645 (C=O), 1609 (C=C); **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.39 (1H, d, *J* = 14.8 Hz, $H_{1''}$), 6.59 (1H, s, H_2), 6.04 (1H, d, *J* = 15.2 Hz, $H_{2''}$), 4.30-4.23 (1H, m, H_5), 3.80 (1H, app. dd, *J* = 10.4, 4.0 Hz, $H_{1'a}$), 3.69 (1H, app. dd, *J* = 10.4, 6.4 Hz, $H_{1'b}$), 3.08 (3H, s, NMe), 3.01 (3H, s, NMe), 2.99-2.97 (2H, m, CH_2SO_2), 2.94 (1H, m, H_{4a}), 2.71 (1H, app. dd, *J* = 15.6, 4.8 Hz, H_{4b}), 1.04-0.99 (2H, m, CH_2Si), 0.87 (9H, s, $C(CH_3)_3$), 0.06 (6H, s, $SiCH_3$), 0.04 (9H, s, $Si(CH_3)_3$); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 167.0, 135.7, 134.6, 120.9, 115.7, 65.2, 62.4, 48.8, 37.5, 36.0, 32.3, 25.9, 18.4, 10.2, -1.9, -5.18, -5.24; **MS** (ESI+) *m/z* 475 ($[M + H]^+$, 100%); **HRMS** (ESI+) *m/z* calcd for $C_{21}H_{43}N_2O_4SSi_2$: 475.2482, found 475.2485; *m/z* calcd for $C_{21}H_{42}N_2O_4SSi_2Na$: 497.2302, found 497.2301

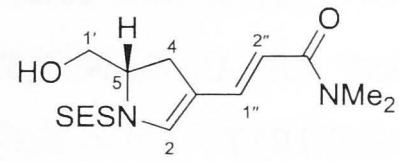
2-Azido-3-methoxybenzoic acid (187)



Preparation of **triflyl azide**: A solution of sodium azide (7.0 g, 108 mmol) in water (16 mL) and dichloromethane (6 m L) was stirred vigorously at 0 °C and then added triflic anhydride (3 mL, 18 mmol) dropwise. The reaction mixture was stirred at this temperature for 2 h and the organic and aqueous phase were separated. The aqueous phase was then extracted using DCM (6 mL) and the combined organic layers were washed with aq. sat. sodium hydrogencarbonate (10 mL) then used immediately in the next step. **(CAUTION – Explosive on concentration. NEVER concentrate.)**

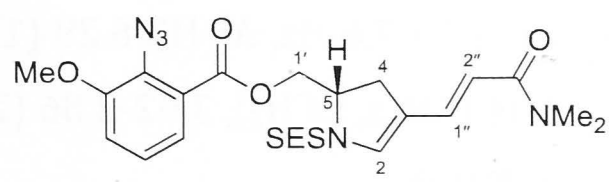
A solution of 2-amino-3-methoxybenzoic acid (1.0 g, 6 mmol) in dichloromethane was added triethylamine (2.5 mL, 18 mmol) and copper sulphate (47.8 mg, 0.3 mmol) in water (0.5 mL). The reaction mixture was cooled to 0 °C and added the freshly prepared solution of triflyl azide (18 mmol) in dichloromethane (12 mL) then methanol (4 mL). The reaction mixture was allowed to warm to rt and stirred at this temperature for a further 1 h. The reaction was quenched by the addition of water (10 mL), acidified with aq. HCl (1 M, 10 mL) and extracted with dichloromethane (2 × 25 mL). The combined organic extracts were dried with Na_2SO_4, filtered and concentrated under reduced pressure. The crude residue was purified by flash chromatography (1% acetic acid in a 2% dichlormethane in methanol solution) to give azide 185 (1.03 g, 89%) as a pale brown solid (m.p. 120 °C). $\mathbf{R_f}$ 0.28 (100% ethyl acetate); **IR** (film) 2975 (C-H), 2162, 2114 (N_3), 1690 (C=O); **^{1}H NMR** (300 MHz, $CDCl_3$) δ 7.73 (1H, dd, *J* = 7.8, 1.5 Hz, Ar-H), 7.20 (1H, t, *J* = 8.1 Hz, Ar-H), 7.10 (1H, dd, *J* = 8.1, 1.5 Hz, Ar-H), 3.96 (3H, s, Ar-CH_3); **^{13}C NMR** (100 MHz, CD_3OD) δ 171.3, 154.0, 128.2, 125.7, 124.9, 116.2, 105.1, 56.7; **MS** (ESI+) *m/z* 164 ([M – N_2]$^-$, 100%), 192 ([M – H]$^-$, 70%); **HRMS** (ESI$^-$) *m/z* calcd for $C_8H_6N_3O_3$: 192.0409, found 192.0409.

(*S*,*E*)-3-(5-(Hydroxymethyl)-1-(2-(trimethylsilyl)ethylsulfonyl)-4,5-dihydro-1*H*-pyrrol-3-yl)-*N*,*N*-dimethylpropenamide (174)



A solution of dimethylacrylamide **171** (23.3 mg, 49.1 μmol) in ethanol (1 mL) was added conc. HCl (0.1 mL) and allowed to stir and rt for 1 h. The reaction mixture was concentrated under reduced pressure and partitioned between an aqueous saturated sodium bicarbonate solution (2 mL) and chloroform (5 mL). The aqueous layer was extracted with chloroform (3 × 5 mL). The combined organic layers were dried with $MgSO_4$, filtered and concentrated under reduced pressure to yield alcohol **174** as a yellow oil. The crude reaction mixture was used in the next step without purification. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.38 (1H, d, J = 15.2 Hz, $H_{1''}$), 6.63 (1H, s, H_2), 6.05 (1H, d, J = 15.2 Hz, $H_{2''}$), 4.34-4.28 (1H, m, H_5), 3.77-3.76 (1H, m, $H_{1'}$), 3.07 (3H, s, NMe), 3.07-3.02 (2H, m, CH_2SO_2), 3.02 (3H, s, NMe), 2.64 (2H, dd, J = 15.6, 5.6 Hz, H_4) 1.03-0.99 (2H, m, CH_2Si), 0.04 (9H, s, $Si(CH_3)_3$); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 166.8, 135.4, 134.7, 120.9, 116.4, 65.6, 63.3, 48.1, 37.5, 36.0, 32.7, 10.2, -1.9.

(*S*,*E*)-(3-(3-(Dimethylamino)-3-oxoprop-1-enyl)-1-(2-(trimethylsilyl)ethylsulfonyl)-4,5-dihydro-1*H*-pyrrol-5-yl)methyl 2-azido-3-methoxybenzoate (185)

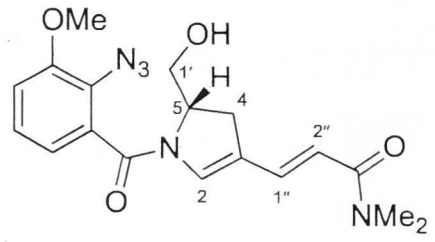


A solution of alcohol **174** (49.1 μmol) in dichloromethane (1 mL) was added acid **187** (11.4 mg, 59.0 μmol), *N*,*N*'-dicyclohexylcarbodiimide (12.1 mg, 58.6 μmol) and 4-dimethylaminopyridine (1.2 mg, 9.8 μmol). The reaction mixture was allowed to stir at rt for 6 h. The reaction mixture was filtered and washed with dichloromethane (3 mL) and concentrated under reduced pressure. The crude mixture was purified by flash chromatography (50%-100% ethyl acetate in hexane) to yield benzoate **185** (22.4 mg, 85% over 2 steps) as a yellow oil. **R_f** 0.41 (100% ethyl acetate); $[\alpha]_D^{20}$ -47.2 (*c* 0.37, $CHCl_3$); **IR** (film) 2953, 2925, 2853 (C-H), 2114 (-N_3), 1727, 1644 (C=O), 1609, 1595 (C=C); **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.43 (1H, d, J = 15.2 Hz, $H_{1''}$), 7.33 (1H, dd, J = 8.0, 1.6 Hz, H_{Ar}), 7.12 (1H, t, J = 8.0 Hz, H_{Ar}), 7.02 (1H, dd, J = 8.4, 1.2 Hz, H_{Ar}), 6.66 (1H, s, H_2), 6.06 (1H, d, J = 14.8 Hz, $H_{2''}$), 4.66 (1H, m, H_5), 4.49 (2H, d, J = 4.8 Hz, $H_{1'}$), 3.91 (3H, s, OCH_3), 3.13 (1H, dd, J = 15.6, 11.6 Hz H_{4a}), 3.07(3H, s, NMe), 3.03-2.99 (2H, m, CH_2SO_2), 3.02 (3H, s, NMe), 2.75

(1H, dd, J = 15.6, 5.2 Hz, H_{4b}), 1.03-0.98 (2H, m, CH_2Si), -0.02 (9H, s, $Si(CH_3)_3$); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 166.7, 165.6, 154.3, 135.3, 134.5, 128.4, 125.2, 124.1, 122.9, 120.6, 116.2, 115.2, 66.5, 59.5, 56.4, 49.3, 37.4, 36.0, 32.8, 10.2, -2.0; **MS** (ESI+) m/z 536 ($[M + H]^+$, 100%); **HRMS** (ESI+) m/z calcd for $C_{23}H_{34}N_5O_6SSi$: 536.1999, found 536.2001; $C_{23}H_{33}N_5O_6SSiNa$: 558.1819, found 558.1817

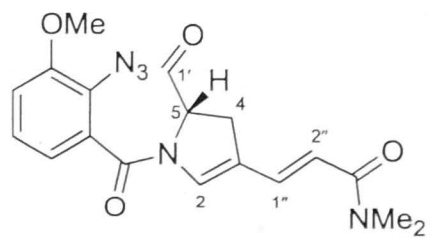
The following compounds could not be fully characterised due to the limited amount of material obtained.

(*S*,*E*)-3-(1-(2-Azido-3-methoxybenzoyl)-5-(hydroxymethyl)-4,5-dihydro-1*H*-pyrrol-3-yl)-*N*,*N*-dimethylpropenamide (75)



A solution of benzoate **185** (3.4 mg, 6.0 μmol) in acetonitrile (2 mL) was added cesium fluoride (7.7 mg, 50.7 μmol) and the mixture was allowed to stir at reflux for 16 h. The reaction mixture was cooled to rt and concentrated under reduced pressure. The crude residue was purified by flash chromatography (5% methanol in ethyl acetate) to yield benzamide **75** (1.4 mg, 59%) as a yellow oil. **R_f** 0.38 (5% methanol in ethyl acetate); **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.30 (1H, d, J = 15.2 Hz, $H_{1''}$), 7.17 (1H, t, J = 8.0 Hz, Ar-H), 6.98 (1H, d, J = 8.4 Hz, Ar-H), 6.90 (1H, d, J = 7.6 Hz, Ar-H), 6.29 (1H, s, H_2), 6.12 (1H, d, J = 15.2 Hz, $H_{2''}$), 4.85-4.77 (1H, m, H_5), 3.94 (3H, s, OCH_3), 3.92-3.86 (2H, m, $H_{1'}$), 3.09 (3H, s, NMe), 3.09-3.01 (2H, m, H_4), 3.01 (3H, s, NMe).

(*S*,*E*)-3-(1-(2-Azido-3-methoxybenzoyl)-5-formyl-4,5-dihydro-1*H*-pyrrol-3-yl)-*N*,*N*-dimethylpropenamide (188)

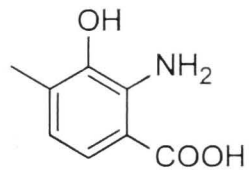


A solution of benzamide **184** (1.4 mg, 3.8 μmol) in dichloromethane (1 mL) was added tetrapropylammonium perutherate (1.5 mg, 4.3 μmol) and *N*-methylmorpholine-*N*-oxide at 0 °C. The reaction mixture was allowed to stir at this temperature for 2 h. The reaction mixture was then filtered through a plug of silica and washed with 10% methanol

in ethyl acetate (10 mL) and 10% methanol in chloroform (10 mL). The filtrate was concentrated under reduced pressure to give aldehyde **188** (1.3 mg, 93%) as a yellow oil. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 8.05 (1H, s, $H_{1'}$), 7.52-7.48 (1H, t, *J* = 8.0 Hz, Ar-H), 7.31-7.26 (1H, m, $H_{1''}$), 7.20-7.16 (1H, m, Ar-H), 7.01-6.93 (1H, m, Ar-H), 6.42 (1H, s, H_2), 6.11 (1H, d, *J* = 14.0 Hz, $H_{2''}$), 5.16-5.09 (1H, m, H_5), 3.94 (3H, s, OCH_3), 3.08 (3H, s, NMe), 3.08-3.03 (2H, m, H_4), 3.03 (3H, s, NMe), with contamination from some residual TPAP, NMO and NMM.

6.5 Experimental procedures for chapter 5

2-Amino-3-hydroxy-4-methylbenzoic acid (193)



Method A:

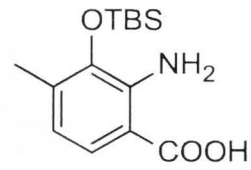
A solution of 3-hydroxy-4-methyl-2-nitrobenzoic acid (210 mg, 1.07 mmol) in methanol (10 mL) was added palladium on charcoal (10% wt, 21 mg) and stirred under a hydrogen atmosphere for 18 h. The reaction mixture was filtered through a pad of Celite™ and concentrated under reduced pressure to yield a red-brown solid. The crude material was purified by subjecting it to a plug of silica (ethyl acetate) to yield a pure sample of amine **193** (155 mg, 87%) as a pink solid.

Method B:

Following a procedure previously reported by Giurg and co-workers,[103] a suspension of palladium on charcoal (10 mg) in distilled water (1 mL) and methanol (2 mL), 1 drop of aq. NaOH (3 M) and potassium borohydride (100 mg, 1.85 mmol) was added 3-hydroxy-4-methyl-2-nitrobenzoic acid (207.9 mg, 1.05 mmol) portionwise at 35-40 °C. The reaction was allowed to stir at this temperature for a further 2 h, filtered and washed with methanol (2 mL). The filtrate was acidified to pH ca. 1 with aq. HCl (1 M) and washed with diethyl ether (3 × 20 mL). The pH of the aqueous phase was then adjusted to pH 2 with aq. NaOH (3 M) and extracted with diethyl ether (3 × 20 mL). The combined organic extracts were dried over $MgSO_4$, filtered and dried under reduced pressure to give a pure sample of the title compound **193** (135.6 mg, 77%) as a pink solid.

m.p. 194 °C (decomp.) (lit.[103] m.p. 234-236 °C, lit.[104] m.p. 213-215 °C) ; **R_f** 0.52 (100% ethyl acetate); **IR** (film) 3700-2400 (OH, NH, COOH), 2953, 2922, 2852 (C-H), 1650 (C=O), 1650, 1610, 1549 (C=C); **^{1}H NMR** (400 MHz, CD_3OD) δ 7.33 (1H, d, *J* = 8.0 Hz, Ar-H), 6.38 (1H, d, *J* = 8.4 Hz, Ar-H), 2.21 (3H, s, Ar-CH_3); **^{13}C NMR** (100 MHz, CD_3OD) δ 171.8, 143.1, 143.0, 130.1, 124.0, 118.6, 110.7, 16.8; **MS** (ESI-) *m/z* 166 ($[M - H]^-$, 20%), 121 ($[M - (H_2O + C{\equiv}O)]^-$, 100%); **HRMS** (ESI+) *m/z* calcd for $C_8H_8NO_3$: 166.0504, found 166.0500

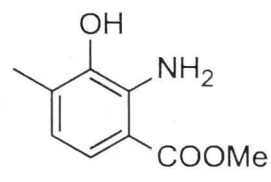
2-Amino-3-(*tert*-butyldimethylsilyloxy)-4-methylbenzoic acid (194)



To a solution of benzoic acid **193** (41.7 mg, 0.25 mmol) in dichloromethane (4 mL) was added *tert*-butyldimethylsilyl chloride (113 g, 0.75 mmol), imidazole (51 mg, 0.75 mmol) and DMAP (3.1 mg, 0.025 mmol) and the reaction was stirred at rt for 16 h. The reaction mixture was added water (5 mL) and extracted with dichloromethane (2 × 10 mL). The combined organic layers were dried with $MgSO_4$, filtered and concentrated under reduced pressure.

The resulting crude mixture was then taken up in tetrahydrofuran (5 mL) and added aq. NaOH (3 M, 3 mL) at rt and allowed to stir at this temperature for 5 mins. The reaction mixture was added aq. HCl (1 M, 10 mL) and extracted with diethyl ether (3 × 15 mL). The combined organic extracts were dried with $MgSO_4$, filtered and concentrated under reduced pressure. The crude material was purified by flash chromatography (gradient elution of 30-50% diethyl ether in hexane) to yield silyl ether **194** (70.1 mg, quant.) as a white solid (**m.p.** 180 °C). $\mathbf{R_f}$ 0.35 (50% diethyl ether in hexane); **IR** (film) 3487, 3380 (NH), 3300-2400 (COOH), 2952, 2929, 2856 (C-H), 1663 (C=O), 1614, 1587, 1533 (C=C); **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.51 (1H, d, *J* = 8.4 Hz, Ar-H), 6.44 (1H, d, *J* = 8.4 Hz, Ar-H), 5.86 (2H, bs, NH), 2.22 (3H, s, Ar-CH_3), 1.06 (9H, s, $C(CH_3)_3$), 0.22 (6H, s, $Si(CH_3)_2$); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 173.5, 144.7, 140.8, 133.9, 124.6, 118.2, 108.0, 26.2, 18.9, 18.1, -3.2; **MS** (ESI+) *m/z* 264 ($[M + H - H_2O]^+$, 282 ($[M + H]^+$, 70%), 320 ($[M + K]^+$, 45%); **HRMS** (ESI+) *m/z* calcd for $C_{14}H_{24}NO_3Si$: 282.1525, found 282.1524

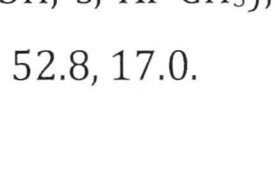
Methyl 2-amino-3-hydroxy-4-methylbenzoate (196)



To a solution of benzoic acid **193** (1.32 mmol) in toluene:methanol (3:2, 10 mL) was added, dropwise, a solution of trimethylsilyldiazomethane (2.0 M in diethyl ether, 920 μL, 1.84 mmol) at 0 °C. The reaction was allowed to warm to rt and stir at this temperature for a further 30 min. The reaction mixture was concentrated under reduced pressure and the to give pure amino ester **196** (176.9 mg, 74%) as a red oil. $\mathbf{R_f}$ 0.21 (10% ethyl acetate in hexane); **IR** (film) 3490, 3379 (NH & OH), 3023 (Ar C-H), 2989, 2951, 2843 (C-H), 1688

(C=O), 1621, 1589, 1543 (C=C); **^{1}H NMR** (400 MHz, CD_3OD) δ 7.39 (1H, d, *J* = 8.0 Hz), 6.42 (1H, d, *J* = 8.4 Hz), 3.84 (3H, s, OCH_3), 2.21 (3H, s, Ar-CH_3); **^{13}C NMR** (100 MHz, CD_3OD) δ 168.9, 141.3, 140.8, 128.2, 123.0, 117.9, 109.8, 51.6, 16.2; **MS** (ESI+) *m/z* 150 ([M + H – MeOH]$^+$, 30%), 182 ([M + H]$^+$, 30%); **HRMS** (ESI+) *m/z* calcd for $C_9H_{12}NO_3$: 182.0817, found 182.0816

Methyl 2-azido-3-hydroxy-4-methylbenzoate (197)



A solution of benzoate **196** (65.8 mg, 0.36 mmol) in aq. HCl (1 M, 2 mL) was added sodium nitrite (52.2 mg, 0.76 mmol) at 0 °C and allowed to stir at this temperature for 30 min. Then, sodium azide (49.2 mg, 0.76 mmol) was added portionwise at 0 °C and the reaction was allowed to stir for a further 1 h. The reaction mixture was then added water (10 mL) and extracted with chloroform (3 × 15 mL). The combined organic extracts were dried with $MgSO_4$, filtered and concentrated under reduced pressure. The crude material was purified by flash chromatography (50-100% diethyl ether in hexane) to provide the azide **197** (58.2 mg, 77%) as a red solid (m.p. 58 °C). **R_f** 0.48 (100% diethyl ether); **IR** (film) 3392 (OH), 3094 (Ar C-H), 3000, 2952, 2918 (C-H), 2131 (N_3), 1709 (C=O), 1617, 1583 (C=C); **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.13 (1H, d, *J* = 7.8 Hz, Ar-H), 6.92 (1H, d, *J* = 7.2 Hz, Ar-H), 3.86 (3H, s, OCH_3), 2.14 (3H, s, Ar-CH_3); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 178.7, 163.3, 139.6, 133.8, 122.5, 119.7 (2C), 52.8, 17.0.

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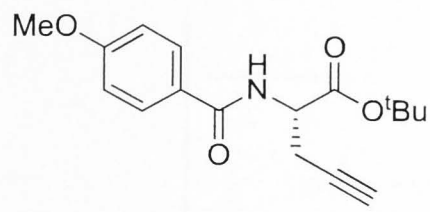
Appendices



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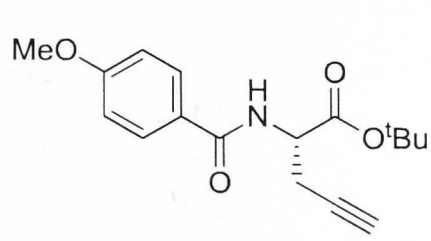

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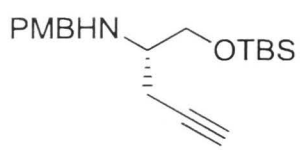

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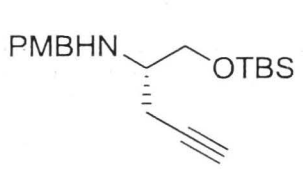

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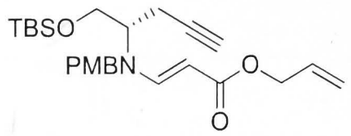

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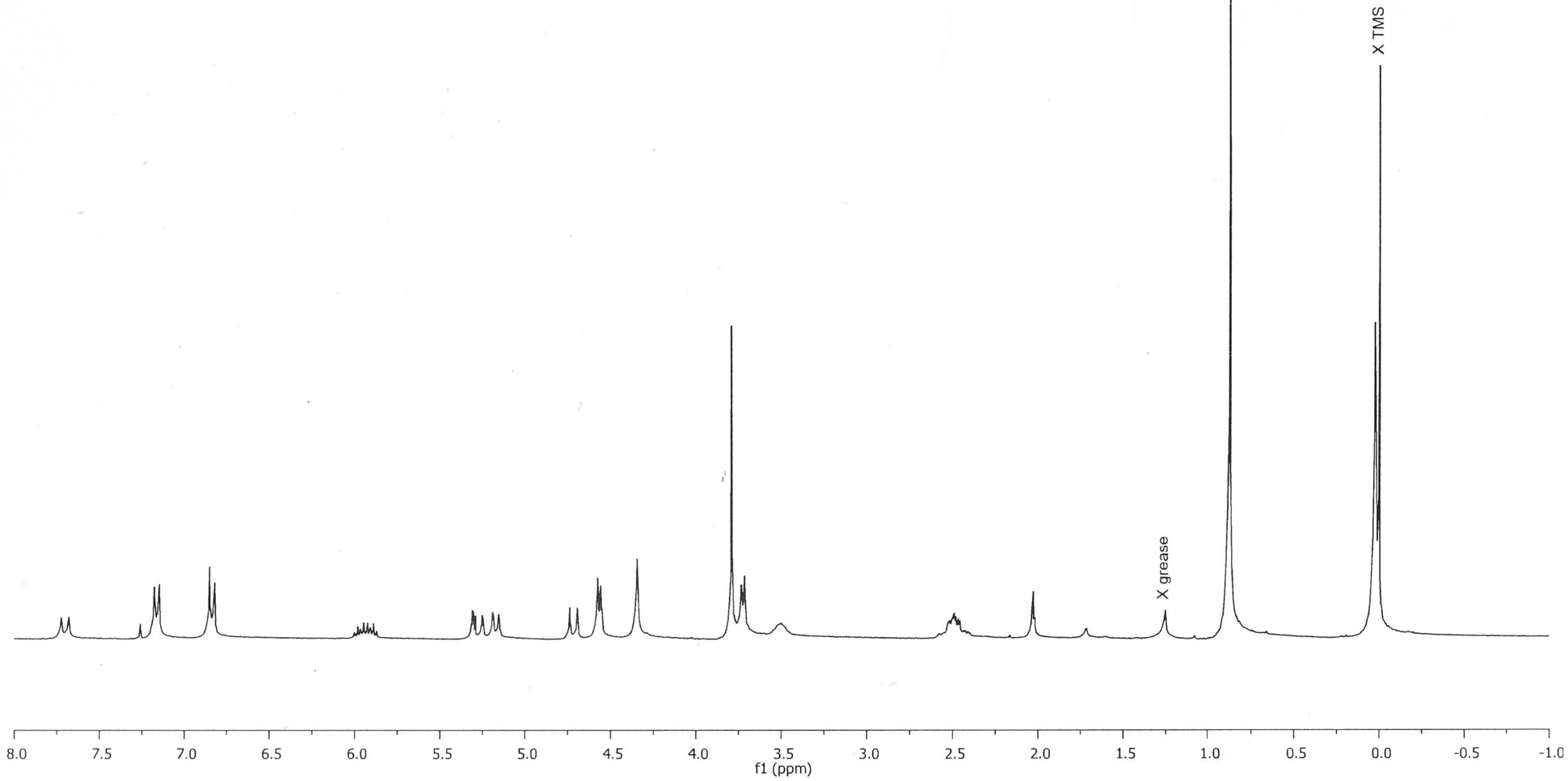

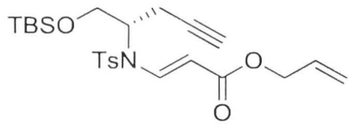

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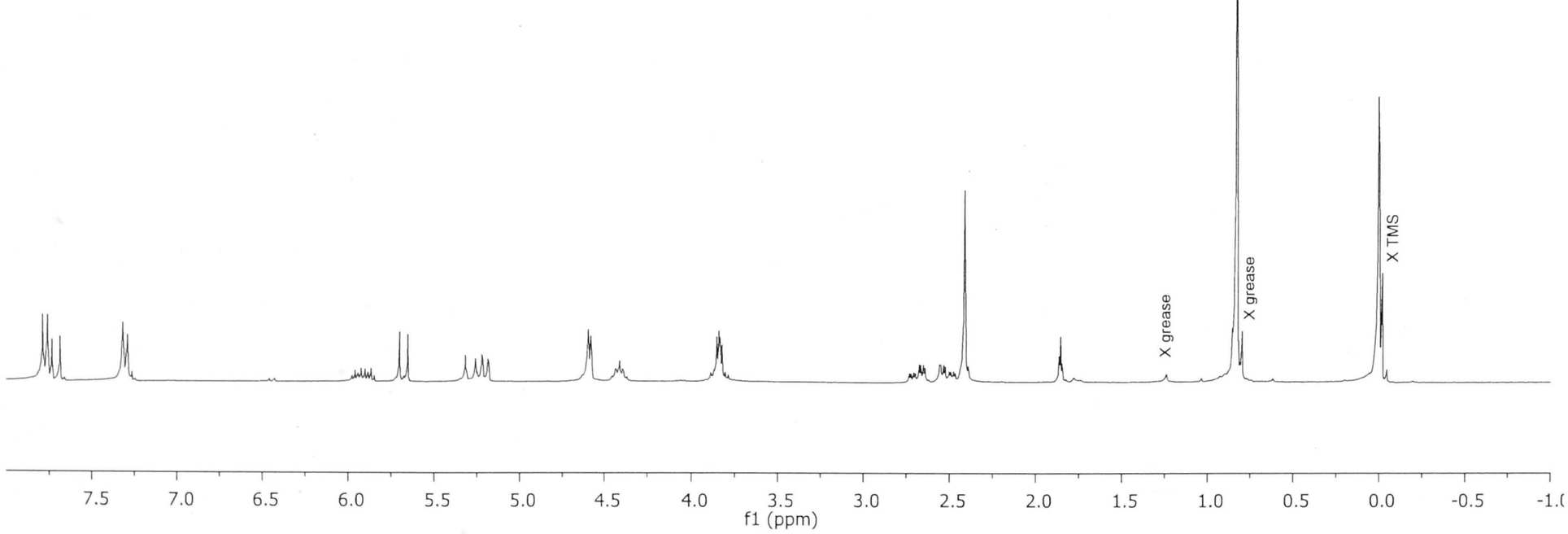

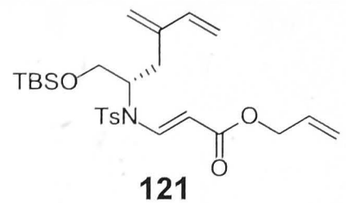

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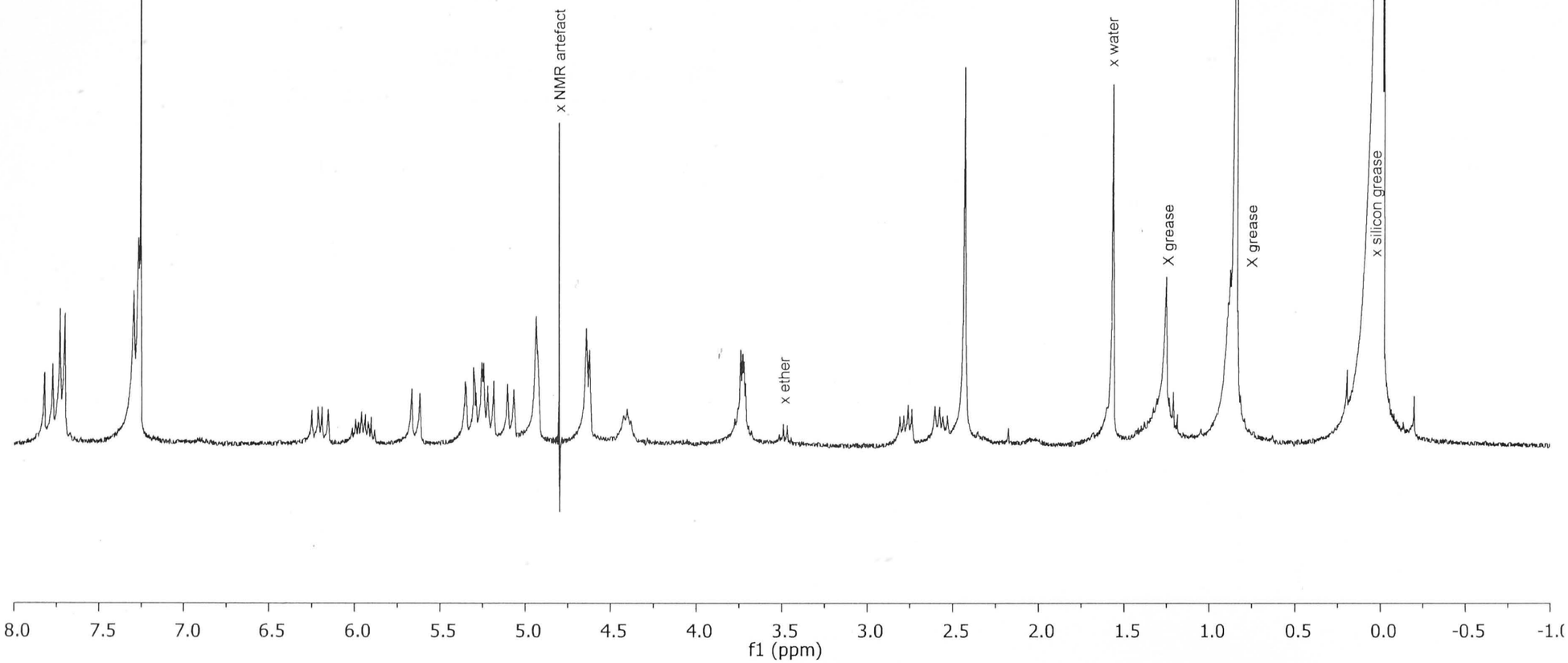

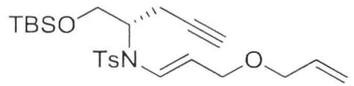

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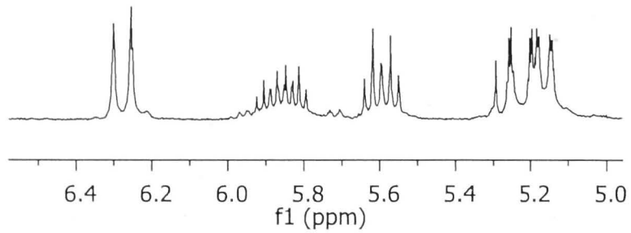

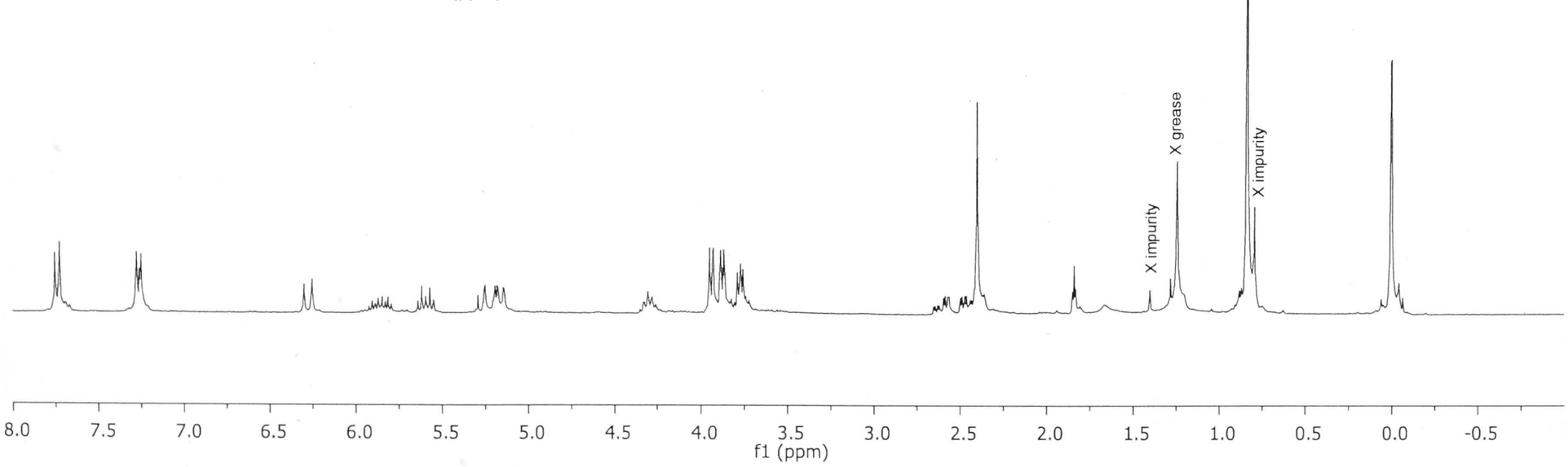

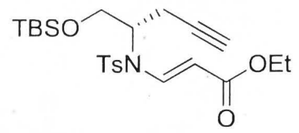

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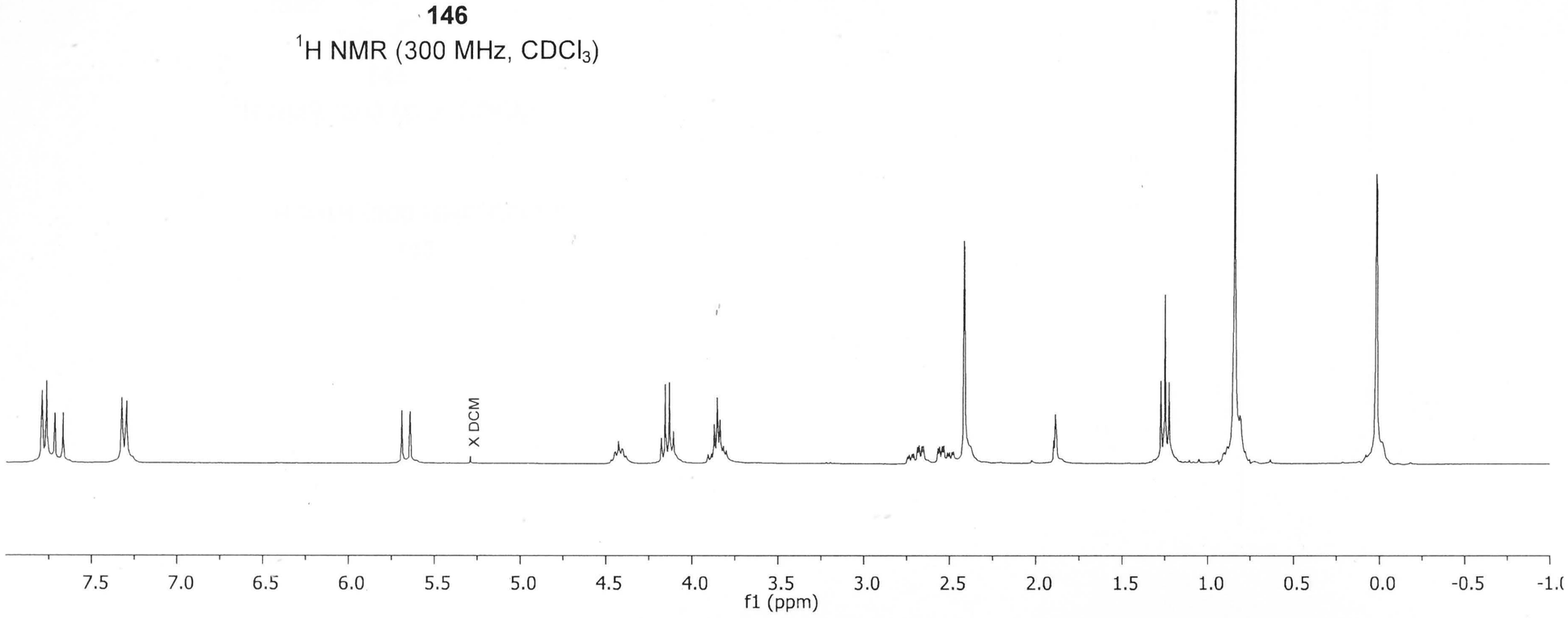

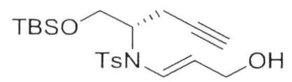

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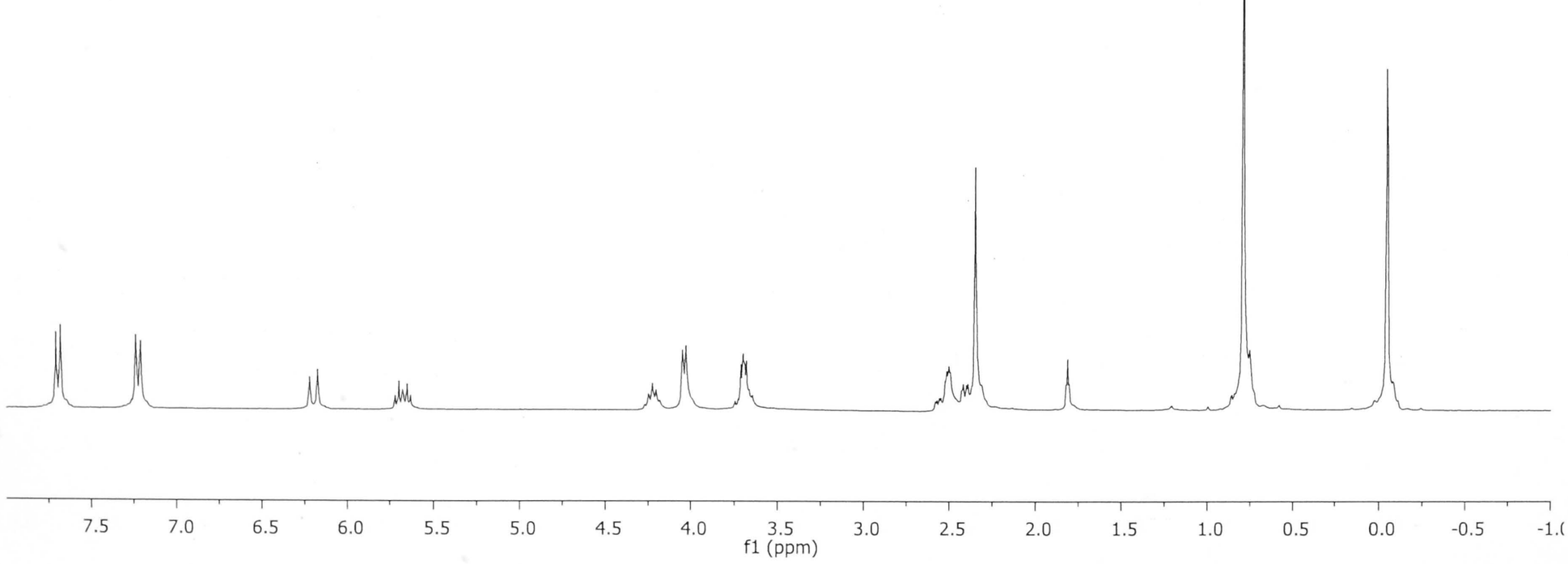

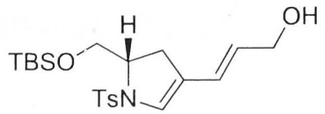

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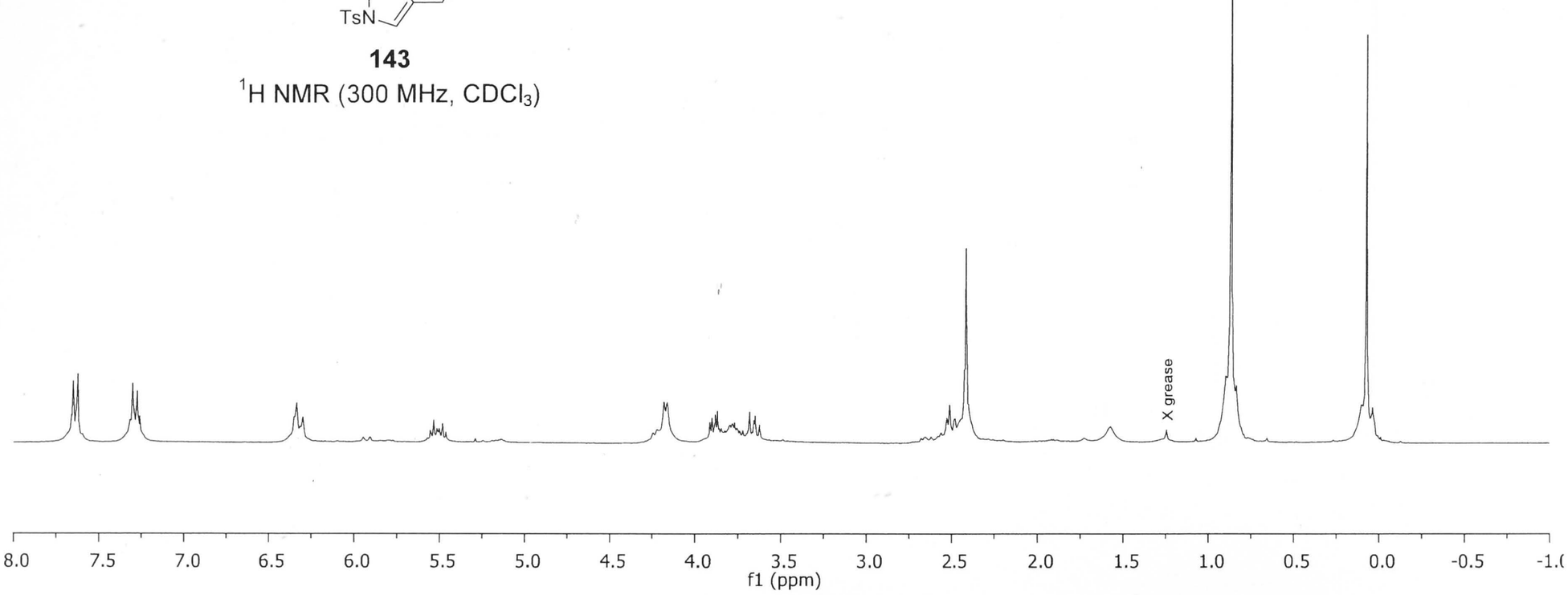

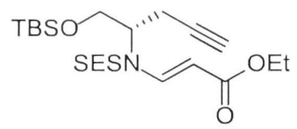

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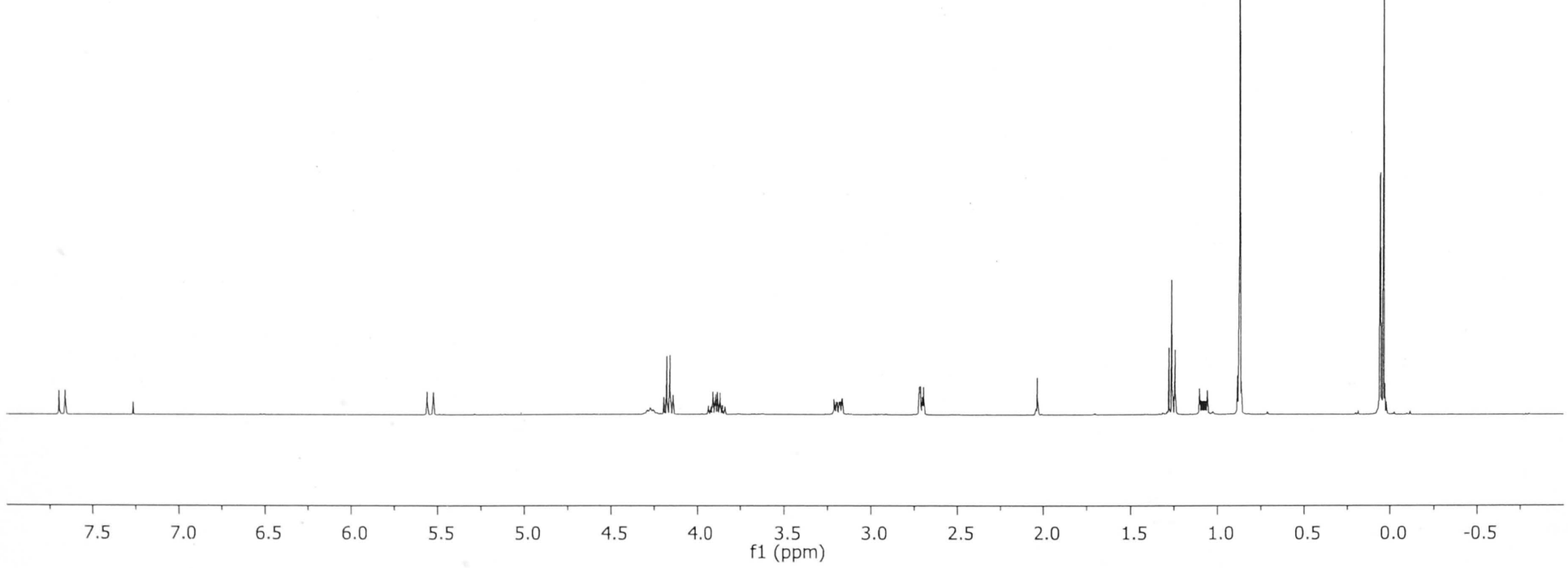

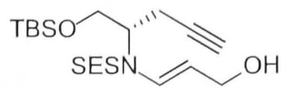

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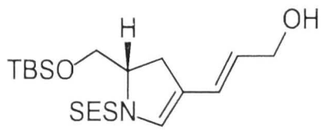

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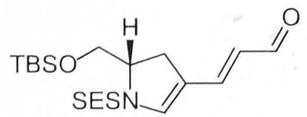

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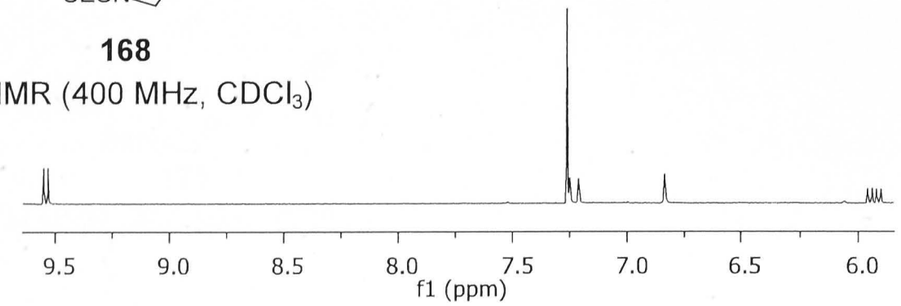

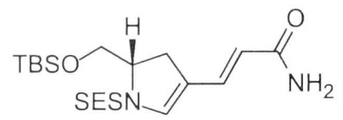

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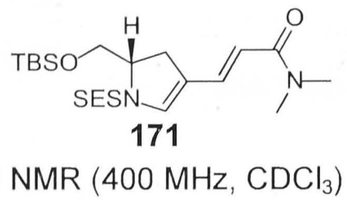

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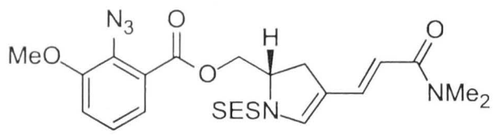
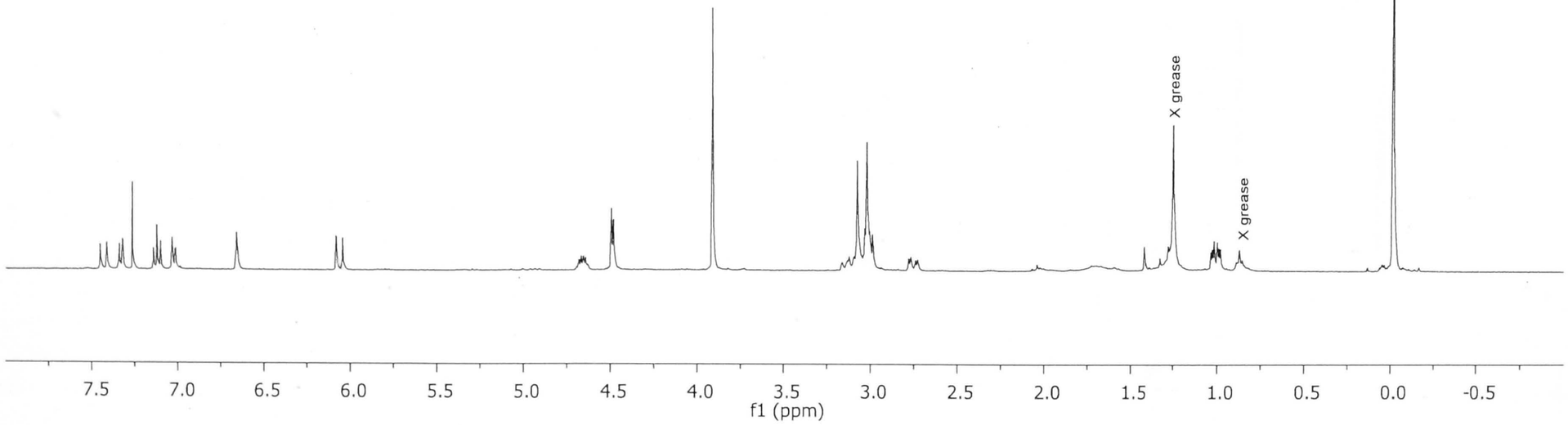
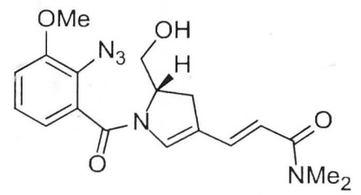


185

^{1}H NMR (400 MHz, $CDCl_3$)





75

^{1}H NMR (400 MHz, $CDCl_3$)